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Report on OPERATION

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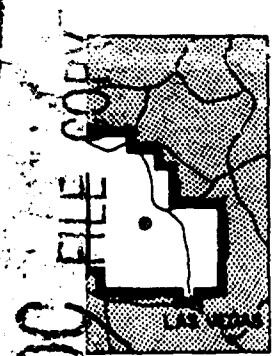

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Project 39.6

BIOLOGICAL EFFECTS OF NUCLEAR RADIATION ON THE MONKEY (Macaca Mulatta)

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Report to the Test Director

BIOLOGICAL EFFECTS OF NUCLEAR RADIATION ON THE MONKEY (Macaca Mulatta)

By
J. E. Pickering
R. W. Zellmer
R. E. Benson
Q. L. Hartwig

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Approved by: R. L. CORSBIE
Director, Program 39
Director, Civil Effects Test Group

School of Aviation Medicine, U. S. Air Force
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September 1958

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ABSTRACT

Macaca mulatta monkeys were exposed to neutron and gamma radiation as one phase of an extensive animal program designed to yield a better understanding of the biological effects of ionizing radiation. Exposure distances were chosen on the basis of dose vs. distance data obtained during Operation Teapot and on the desired biological responses. In both shots in which Project 39.6 participated, the radiation dose required to produce death in 30 days in 50 per cent of the animals was determined. All animals were followed for acute radiation effects, and, where no mortality occurred, they are being followed for long-term effects, such as cataract production, bone-marrow change, shortening of life span, and carcinogenesis. Ultimately the long-term findings will be compared with known human data.

ACKNOWLEDGMENTS

The authors wish to acknowledge the excellent cooperation and advice obtained from participants in Projects 39.1, 39.5, 39.7, and 39.7a; without this free exchange of data, equipment, and personnel, such an undertaking could not have been accomplished. In this same regard, the over-all supervision and administrative support furnished by members of the Civil Effects Test Group staff, under the direction of R. L. Corsbie, as well as Program 39, contributed immeasurably to the success of the work. During the early stages of the entire study, W. H. Langham, W. T. Ham, and K. Z. Morgan gave generously of their time.

The School of Aviation Medicine personnel responsible for the over-all support deserve special mention.

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Chapter 1

INTRODUCTION

The paucity of adequate data on both the acute and chronic effects of ionizing radiation has necessitated a continuing program of investigation on permissible limits of exposure as well as threshold-dose determinations. Accidental exposure of individuals on several occasions has demonstrated certain unfavorable effects and has placed a requirement on determining long-term prognosis following exposure to ionizing radiation.

Certain biologic end points of concern among human survivors of accidental exposures can be observed in the monkey under conditions of similar exposure. For example, laboratory experiments involving pure neutron, pure gamma, and mixed neutron-gamma radiation have produced early lens abnormalities, mature cataracts, and bone-marrow changes in the monkey. Also, more recently, evidence has been found indicating that brain tumors may be radiation induced. It therefore becomes obvious that a better understanding of radiation effects is imperative so long as individuals continue to be exposed to, and work with, radiation sources. This study is a continuation of the series of long-term studies mentioned above which are currently seven years postirradiation.

1.1 OBJECTIVES

The primary objective of Project 39.6 was to correlate neutron and gamma measurements with biological response. This was accomplished by so arranging the exposure pattern that (1) the dose required to produce 50 per cent lethality in 30 days could be determined, in addition to an evaluation of the survival time vs. dose relation; (2) the range of doses would permit studies on acute clinical signs, such as purpura, anorexia, retching, vomiting, epilation, iritis, retinal edema, diarrhea, and fatigue; and (3) a sufficient number of low-dose exposures would be obtained to allow many animals to be followed for several years to determine the incidence of long-term acute effects, such as cataract production, life-span shortening, bone-marrow changes, and carcinogenesis.

1.2 BACKGROUND

For several years attempts have been made to predict the effects of ionizing radiation on man, particularly when the doses may be higher than the present-day tolerance limits. Dose schedules just below the point at which minimal biological change will take place are becoming increasingly important in nuclear propulsion programs for both manned and unmanned vehicles. In an attempt to develop guidelines for these programs, a series of acute, as well as chronic, experiments was begun using the rhesus monkey because of his relatively long life

expectancy (25 years) and his apparent similarity to man in certain physiological and psychological responses. Acute localized exposures to fast-neutron, thermal-neutron, and gamma radiation have been accomplished.[1] In each instance mature cataracts have been produced; in certain instances bone-marrow changes[2] and brain tumors[3] have been produced; and in a few cases radiation deaths have been produced. At the same time other animals were exposed to whole-body radiation in small fractionated doses over fairly long periods of time. Again lens changes were observed along with bone-marrow changes; but, to date, no deaths have occurred in this latter group which were attributable solely to radiation effects. Throughout the entire program, however, no acute whole-body studies had been developed in sufficient proportions to be meaningful statistically; consequently, participation in Operation Plumbbob has contributed materially to a better understanding of the acute and long-term biological effects of acute doses of radiation.

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3. S. P. Kent and J. E. Pickering, Neoplasms in Monkeys (Macaca Mulatta): Spontaneous and Irradiation Induced, School of Aviation Medicine, USAF, Report 57-110, June 1958; Cancer, 11(1): 138-147 (January–February 1958).

Chapter 2

PROCEDURE

2.1 SHOT PARTICIPATION

Project 39.6 participated on two shots* of the Operation Plumbbob series. These shots were optimal for animal exposures on the basis of yield, cab shielding, and geographical location. The first shot, Wilson, was a 10-kt (±5 per cent) high-neutron-yield device detonated at 500 ft from a balloon in Area 9. The second shot, Fizeau, was an 11-kt (±20 per cent) high-neutron-yield device detonated from a 500-ft tower in Area 3.

2.2 STATION PLACEMENT AND FIELD EXPOSURE

The monkey exposure stations for the Wilson shot were arranged along a radial line east-southeast of the balloon in Area 9 on a bearing of 120°. For the Fizeau shot all stations were located approximately south of the working point within an angle of 15° to the west and 5° to the east of a line drawn from station 3-300 through the working point. Along these lines there was no perturbing material between the device and the stations. The distances of the individual stations (Table 2.1) from Ground Zero (GZ) were chosen on the basis of dose-prediction data obtained on Operation Teapot for dose vs. biological response.[1]

The blast containers used in the biological experiments of Operation Greenhouse[2] were modified so that they would, when bolted in pairs, accommodate eight individual holding cages for the monkeys (Fig. 2.1). The blast cans were anchored with ⅛-in. cable to prevent displacement from blast and were painted with aluminum paint to reflect heat.

2.3 INSTRUMENTATION

All dosimetric measurements and pretest calibrations were made by Projects 39.1 (gamma dosimetry) and 39.5 (neutron dosimetry). The neutron measurements were made using the fission-foil system of Hurst,[3] including gold foils for the thermal neutrons and sulfur foils for high-energy neutron measurements. The gamma-ray measurements were made using the USAF chemical dosimeter system developed by Sigoloff.[4] In this test series the gamma-ray dosimeters were modified somewhat from those used in Operation Teapot.[1] The dosimeters consisted of tetrachloroethylene overlayed with a water-dye solution that had approximately 10 per cent of the volume of the halogenated hydrocarbon. The whole system was encased in

* Animals were also placed in the field for the Franklin event; however, no biological data were obtained because of partial failure of the test device.

an aluminum can, with lithium metal surrounding the chemical dosimeters in all directions to eliminate the increased low-gamma-energy sensitivity of the system and to reduce the response to thermal neutrons (Fig. 2.2).

TABLE 2.1—EXPOSURE DISTANCE

Station	Distance from GZ, yd	
	Wilson	Fizeau
A	1325	1425
B	1350	1450
C	1375	1475
D	1400	1500
E	1425	1525
F	1450	1550
G	1475	1575
H	1500	1600
I	1525	1625
J		1650

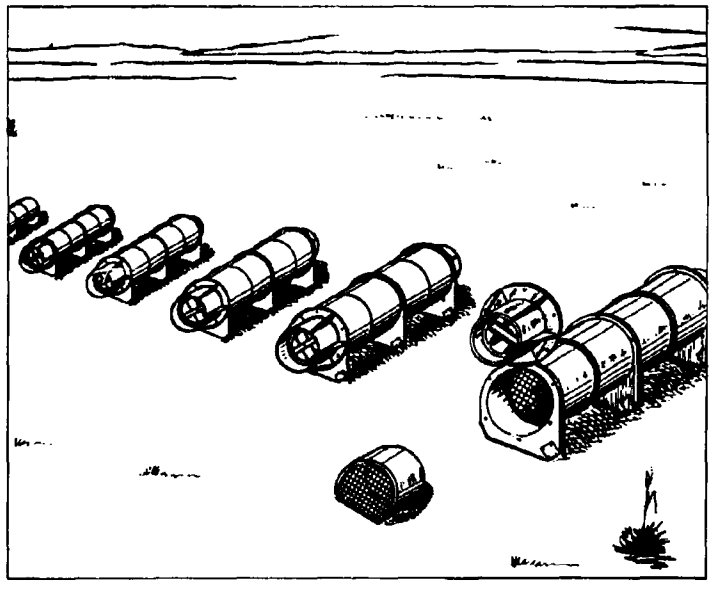

Fig. 2.1—Exposure arrangement for animals.

Every other animal was monitored with chemical dosimeters for gamma-ray dose determinations, and one set of threshold detectors was placed in each of the 10 large blast cans, in addition to the over-all area dosimetry coverage of Project 39.5.

2.4 BIOLOGICAL MEASUREMENTS

In both shots there were three major end points: (1) the determination of a radiation dose that produces death in 50 per cent of the animals in 30 days and an evaluation of the survival time vs. dose relation; (2) a careful clinical evaluation of all the animals with respect to doses

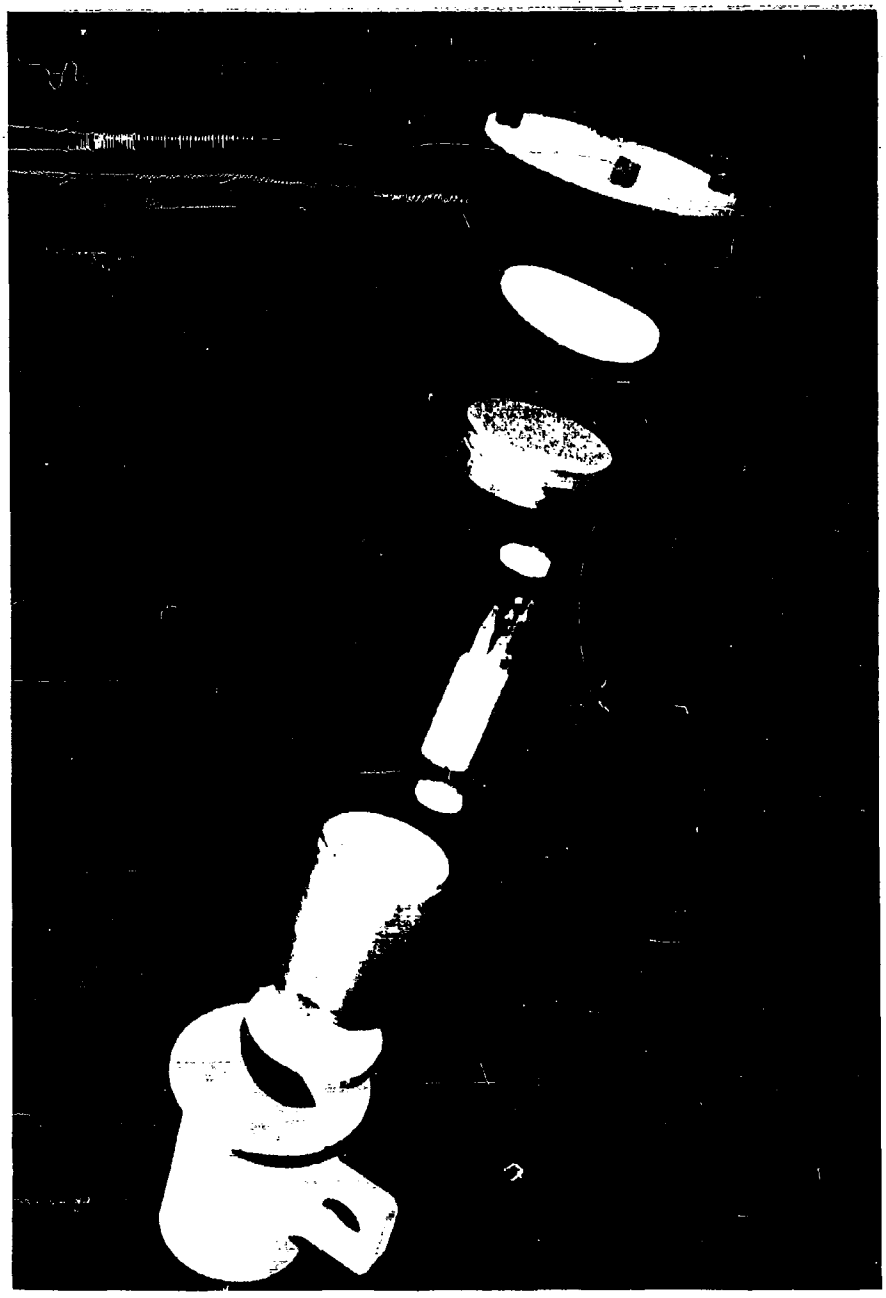

Fig. 2.2—Chemical dosimeters and holders.

that produced erythema, epilation, retching, vomiting, diarrhea, iritis, retinal edema, weight loss, fatigability, etc.; and (3) obtaining sufficient survivors to integrate into a long-term follow-up program on the latent effects of ionizing radiation. The long-term group will be watched for cataract production, life-span shortening, and increased incidence of leukomia and other carcinogeneses.

Two additional biological measurements were obtained on the Wilson shot. Prior to transfer to the Camp Mercury site, one subgroup was injected with Fe^{59} so that, following sublethal

TABLE 2.2—DOSIMETER DISTANCE (YARDS) FROM GZ

Station	Wilson shot		Fizeau shot	
	Air	Container	Air	Container
A	500	1325	500	1425
B	750	1350	750	1450
C	1000	1375	1000	1475
D	1250	1400	1250	1500
E	1500	1425	1500	1525
F	1750	1450	1750	1550
G	2000	1475	2000	1575
H		1500		1600
I		1525		1625
J				1650

doses of radiation, hematopoietic damage and recovery could be determined by measuring the uptake of Fe^{59} by the irradiated bone marrow. A second subgroup received gold dental inlays several months before arriving at the Forward Area, and, following a lethal dose of radiation, this group was studied for neutron activation of the gold vs. measured neutron dose.

2.5 PHYSICAL MEASUREMENTS

Ionizing radiation fluxes at various distances were measured using the dosimetric devices furnished by Projects 39.1 and 39.5. The locations of the dosimeters along the two exposure radial lines, as well as those inside the blast containers, are listed in Table 2.2.

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2. R. H. Draeger et al., Operation Greenhouse Report, WT-15, Annex 2.3, August 1951.
3. G. S. Hurst et al., Operation Plumbbob Report, WT-1504, March 1958.
4. S. C. Sigoloff et al., Operation Plumbbob Report, ITR-1500, May 1958.

Chapter 3

RESULTS

3.1 BIOLOGICAL MEASUREMENTS

3.1.1 Lethality

Recent unpublished data indicate that the mean energy of bomb-spectrum gamma radiation is very close to that of Co^{60} gamma radiation.[1] Therefore it was felt that a base-line laboratory study of the parameters of survival time and median lethality vs. whole-body dose of Co^{60} gamma radiation was necessary in order to evaluate the relative biological effectiveness (RBE) of bomb-spectrum neutron flux. Such a study was performed using approximately 7500 curies of Co^{60} which yielded a dose rate of 800 r/min. From these data an RBE for survival time in the region below 1500 r of gamma was calculated to be 1.33 ± 0.09 for Fizeau shot and 1.27 ± 0.33 for Wilson shot. If the data from the two test shots are combined, the RBE is calculated to be 1.29 ± 0.19.

From these RBE's the dose that would kill 50 per cent of the animals in 30 days (LD_{50}^{30}) was found by probit analysis to be 473 rem for Wilson shot, 522 rem for Fizeau shot, and 486 rem for the Wilson and Fizeau shots combined. Chi-square results are 0.61 with 2 degrees of freedom, 5.66 with 5 degrees of freedom, and 10.66 with 7 degrees of freedom, respectively. Thus a high degree of confidence cannot be ascribed to these median lethal doses.

In Table 3.1 are shown the results of the lethality studies. The rep doses are taken from a least-squares regression line of the D vs. log RD^2 plot of measured gamma and neutron fluxes (see Secs. 3.2.1 and 3.2.2) and are converted to rem using the calculated RBE's of 1.33 and 1.27. The survival times are the antilogs of mean log survival times of each group. The regression lines of mean log survival time on log dose have been tested for reliability of fit with the "F" statistic and show a significance at the 0.01 level.

The mortality resulting from nuclear radiation during the first 30 days following exposure is shown in Figs. 3.1 to 3.3. Total 30-day mortality was 87.4 per cent on Wilson shot and 27 per cent on Fizeau shot. Two significant peaks were observed in the daily mortality for the Wilson event, the first on D+7 day and the second on D+14 day. On Fizeau only the 14-day peak was apparent. The antilogs of the mean log survival times for each dose group in Wilson and Fizeau shots are plotted against dose in Fig. 3.4, and the regression line for these data is shown.

3.1.2 Clinical Observations

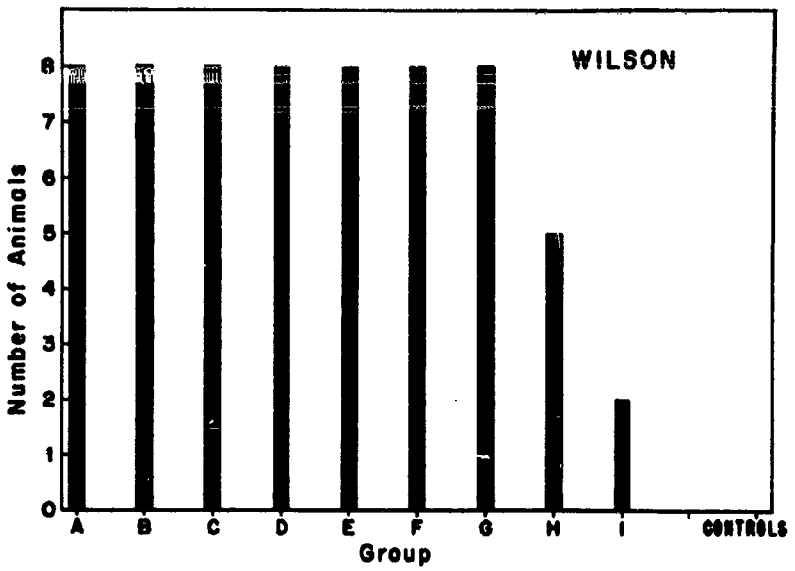
The clinical observations are summarized in Figs. 3.5 to 3.10. The findings reported, in addition to being typical of radiation injury, may permit an interesting comparison between the biological response of man and monkey to similar radiation doses at comparable distances.

(Text continues on page 22.)

TABLE 3.1—RADIATION PARAMETERS

Group	Dose* (γ), rep	Dose* ($_{n}n^{1}$), rep	Rem†	Slant range, yd	Survival time, hr	Survivors‡ (30 day)
			Wilson			
A	522	516	1177	1336	187	0
B	470	446	1036	1360	201	0
C	423	386	913	1385	205	0
D	381	334	805	1410	265	0
E	344	290	712	1435	320	0
F	310	251	629	1460	351	0
G	281	219	559	1484	422	0
H	254	191	497	1509	406	3
I	230	166	441	1534	456	6
J						
Control	0	0	0	0	0	8
			Fizeau			
A	319	270	678	1435	321	0
B	286	234	597	1460	299	2
C	257	205	530	1484	358	6
D	230	177	465	1509	345	5
E	206	154	411	1534	0	8
F	185	134	363	1559	549	7
G	166	116	320	1584	0	8
H	149	101	283	1609	0	8
I	134	88	251	1634	0	8
J	120	76	221	1659	632	7
Control	0	0	0	0	0	8

*From plot of D vs. log $RD^{\frac{1}{2}}$.
†RBE calculated, 1.27 ± 0.33 (Wilson) and 1.33 ± 0.09 (Fizeau).
‡Antilog of mean log survival time.



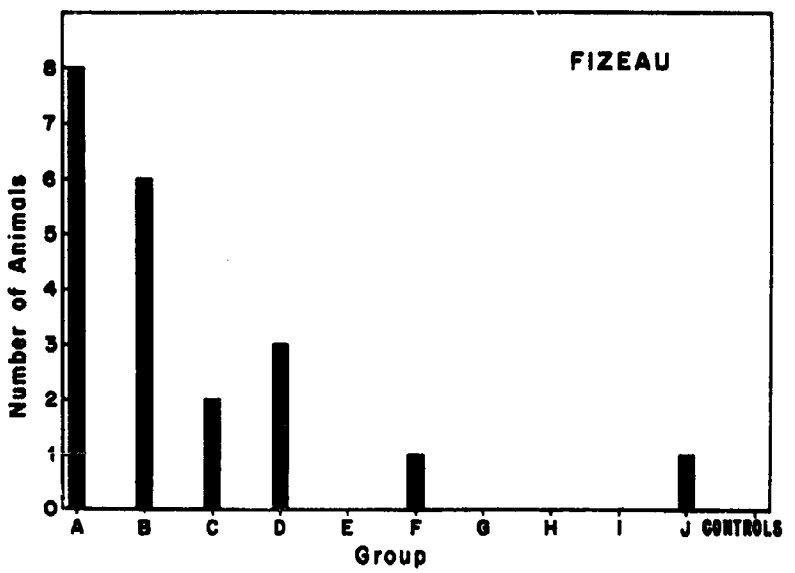


Fig. 3.1 —Thirty-day mortality.

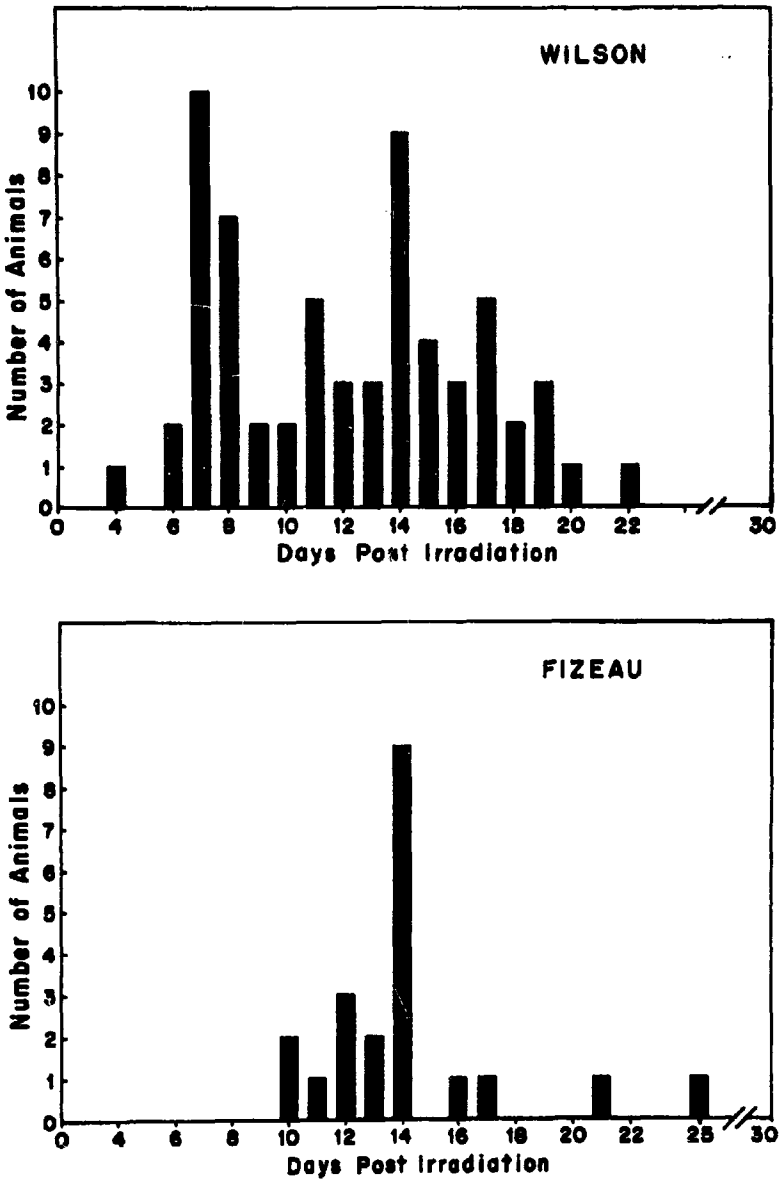
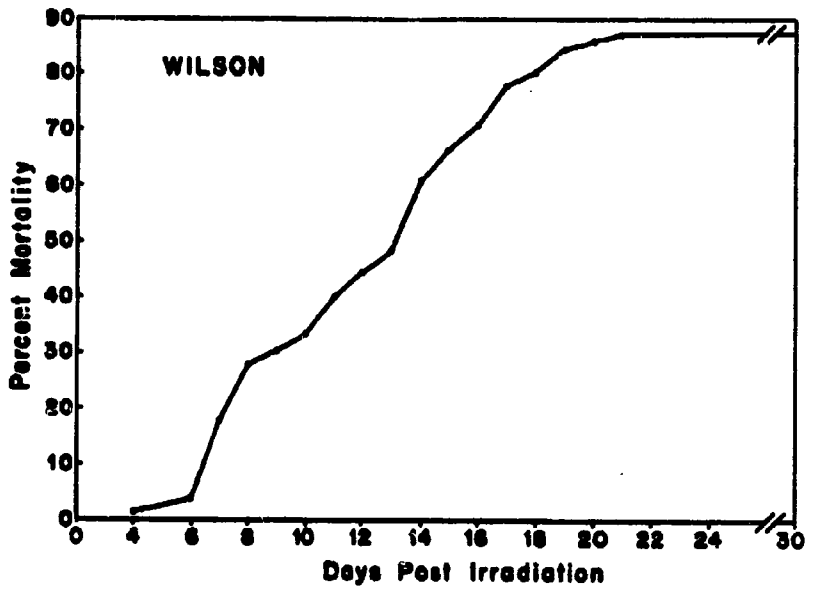


Fig. 3.2—Daily mortality.



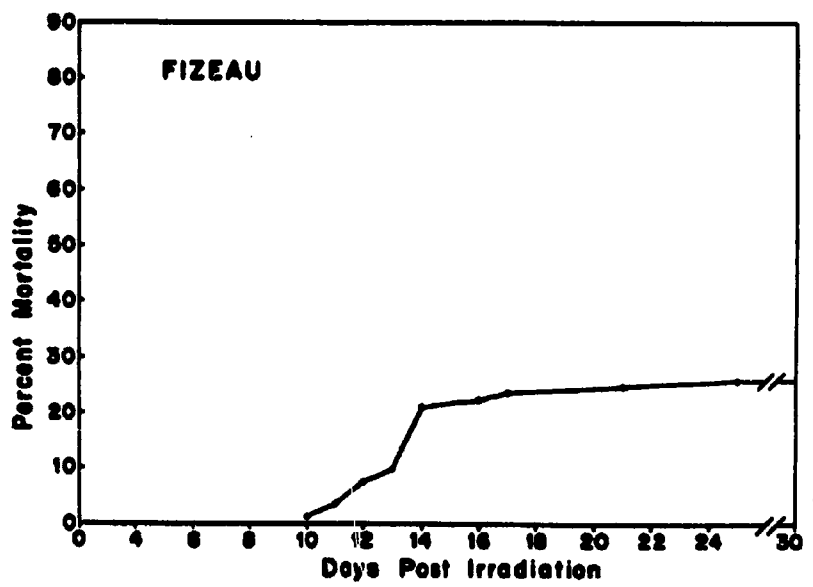


Fig. 3.3—Accumulated mortality.

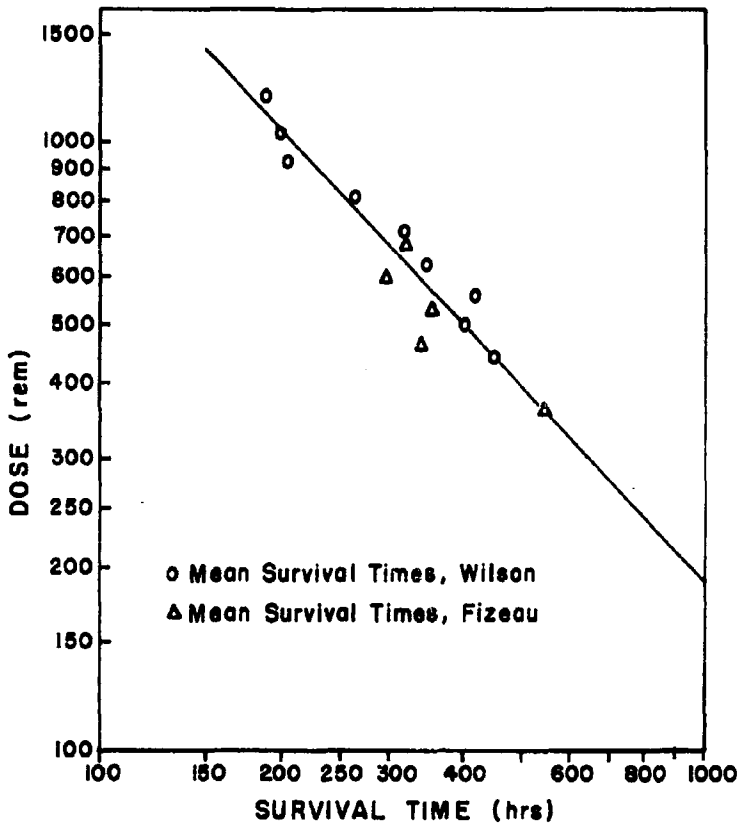
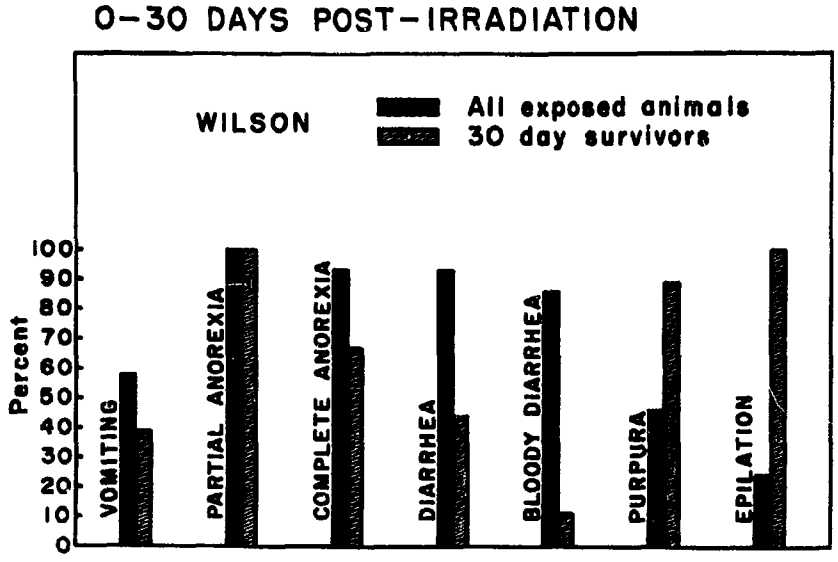


Fig. 3.4—Survival time.



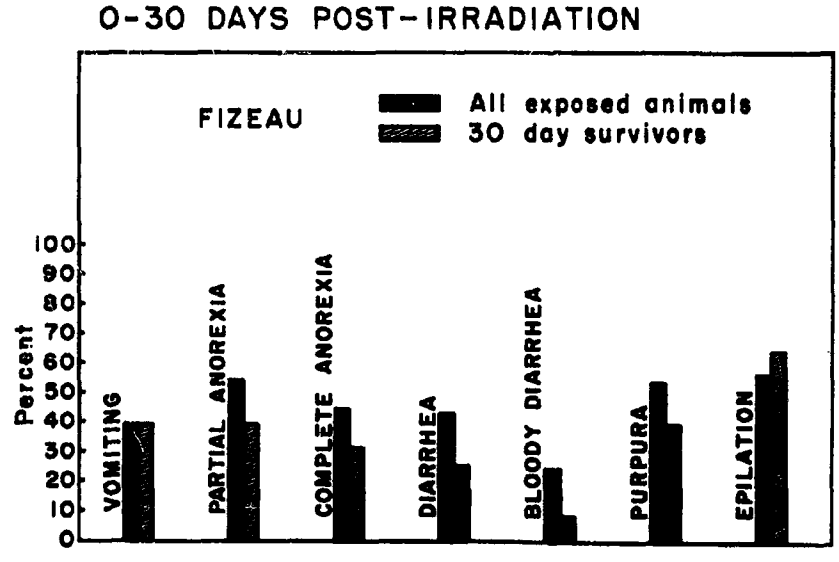


Fig 3.5—Incidence of clinical symptoms.

Vomiting was observed in 58.3 per cent of all Wilson shot animals within 2 hr following exposure and in 36.3 per cent of all 20-day survivors during this same period. The Fizeau shot demonstrated a 39 per cent incidence of vomiting in all exposed animals; the percentage by group is shown in Fig. 3.6. Vomiting was not observed in any animals later than 2 hr post-exposure.

Anorexia was observed in all Wilson animals at some period during the first 21 days postirradiation; whereas only 50 per cent of the Fizeau animals demonstrated complete anorexia. The greatest incidence of anorexia was observed during the 2- to 9-day period following irradiation. Complete loss of appetite was invariably observed in these animals prior to death.

Epilation was first definitely observed in the animals 13 to 15 days postirradiation; the last case to develop was observed on the 21st and 26th days (Fig. 3.7). It is possible that radiation-induced epilation began earlier than is indicated but was masked by normal shedding, which was occurring in these animals prior to irradiation.

Purpura was first observed on the 10th and 11th days postirradiation and developed rapidly in surviving animals (Fig. 3.8). The total incidence of purpura in 30-day survivors was 91 per cent for Wilson animals and 39 per cent for Fizeau animals (Fig. 3.5). Subcutaneous and cutaneous hemorrhages were widely distributed over the body, most frequently involving the face, arms, chest, legs, and flexor surfaces.

Diarrhea occurred in 93 per cent of all animals exposed; and bloody diarrhea developed, usually in the terminal stages, in 86 per cent of the Wilson animals. In the 30-day survivors diarrhea occurred in 30 per cent, and bloody diarrhea developed in 10 per cent. The incidence of diarrhea and bloody diarrhea in Fizeau animals during the 0- to 30-day period postirradiation was 40 per cent (Fig. 3.9).

The body weights of the animals two months prior to, and 30 days subsequent to, exposure on Wilson shot are shown in Fig. 3.10. Note that the control group exhibits a general increase in mean body weight; whereas the experimental group exhibits an initial increase, followed by a marked drop in mean body weight which continues through the 30-day period of the study. The Fizeau animals (Fig. 3.10) demonstrated only a very slight change in body weight.

3.1.3 Iron Metabolism and Hematology

The results of the Fe^{59} and hematology studies are shown in Table 3.2 and Figs. 3.11 to 3.15. With either intravenous or intraperitoneal injection, certain iron compounds can be utilized by the hematopoietic system of specific mammals in the synthesis of hemoglobin in the erythrocytes. Hematopoietic incorporation of injected iron has been shown to be preferential to utilization of iron from the animal's body pool of iron. In the normal animal excess Fe^{59} injected is substantially cleared from the plasma within a few hours after injection. Radioactivity that subsequently appears in the circulating blood is almost completely limited to the erythrocytes. Radioiron activity in circulating blood at specific times postinjection has consequently been construed to reflect the rate of incorporation of injected iron by the erythropoietic system, and thus it functions as an index of hematopoietic activity.

3.1.4 Behavioral Changes

The behavioral syndrome for the monkey following exposure to bomb radiations is shown in Figs. 3.16 to 3.18. The results are comparable to those reported following exposure to X rays. The behavioral categories studied were (1) nondirected visual activity (predominance of visual activity without apparent fixation), (2) nondirected locomotor activity (whether by bouncing, pacing, or swinging suspension), (3) object-directed activity (whether by visual, manual, or oral response to the cage parts or to the experimenter), and (4) self-directed activity (whether by visual, manual, or oral response to the subject's own body).

3.1.5 Pathological Findings

The anatomical material in this section of the report was gathered from shot Fizeau. Of the 80 animals exposed, 22 died, the first death occurring on the 11th postirradiation day and

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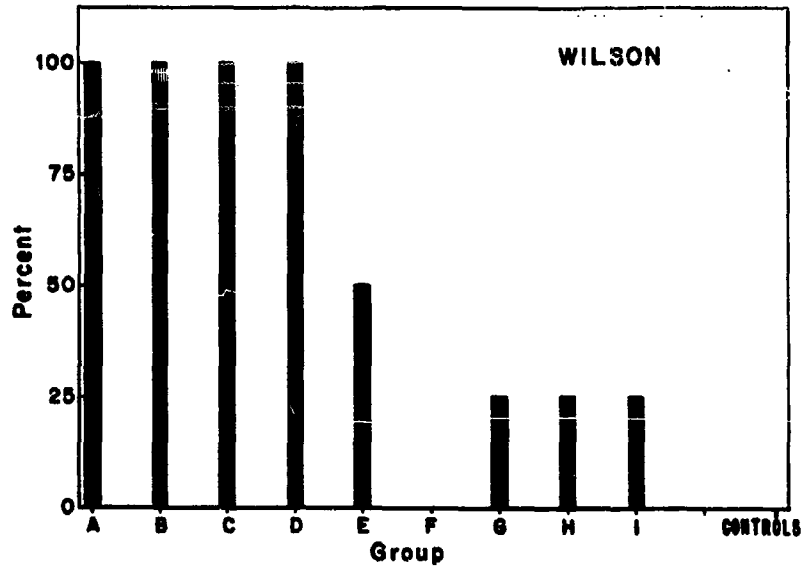


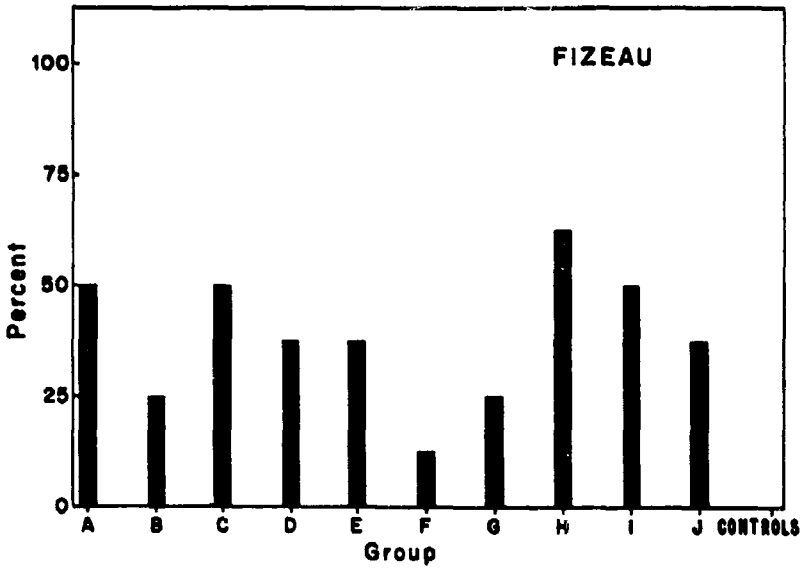
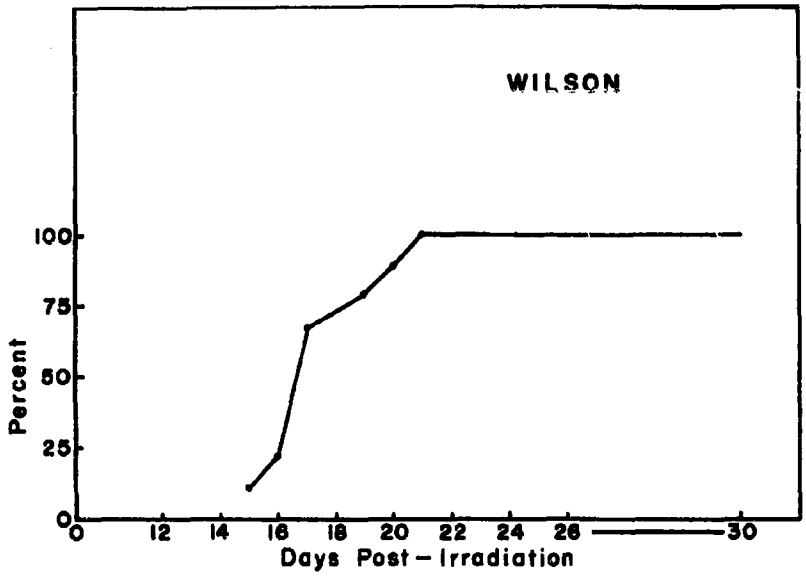


Fig. 3.8—Vomiting (0 to 2 hr postirradiation).



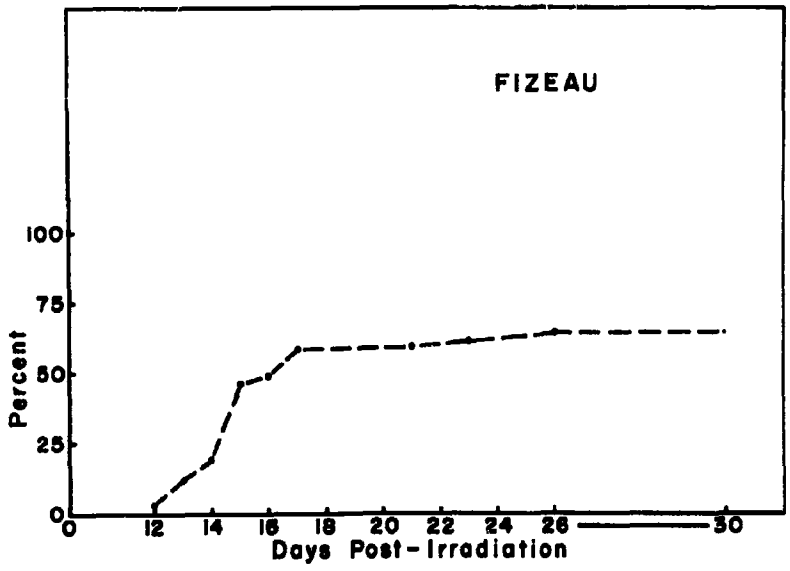
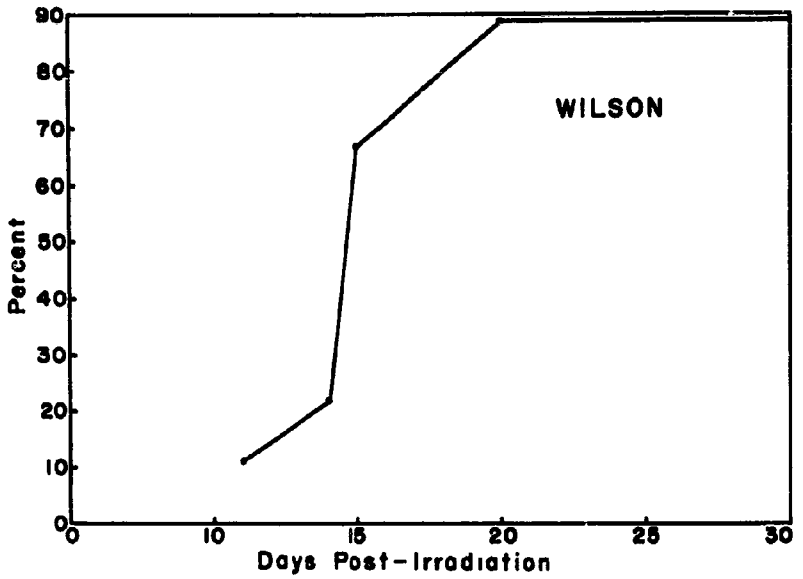


Fig. 3.7—Epilation (30-day survivors).



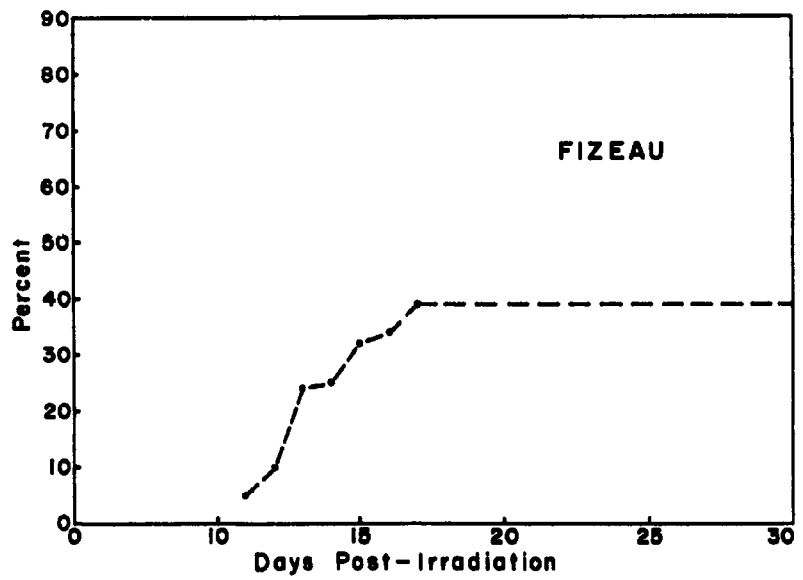


Fig. 3.8—Purpura (30-day survivors).

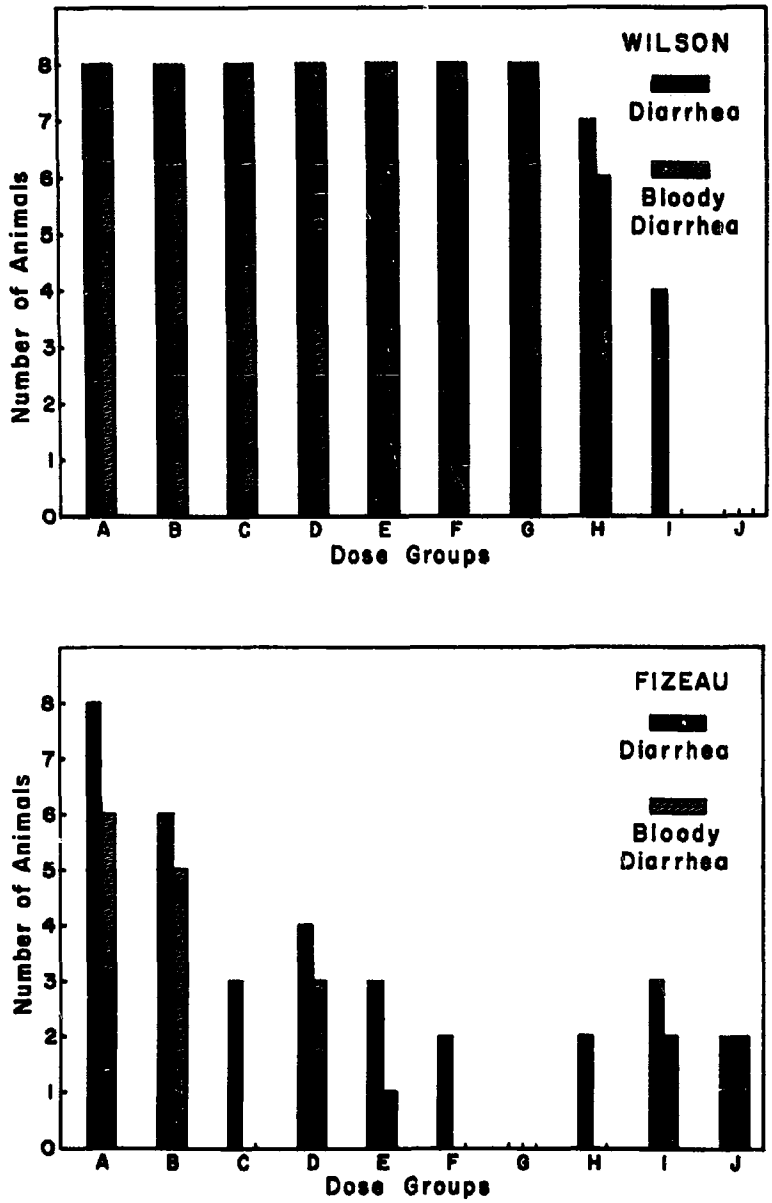
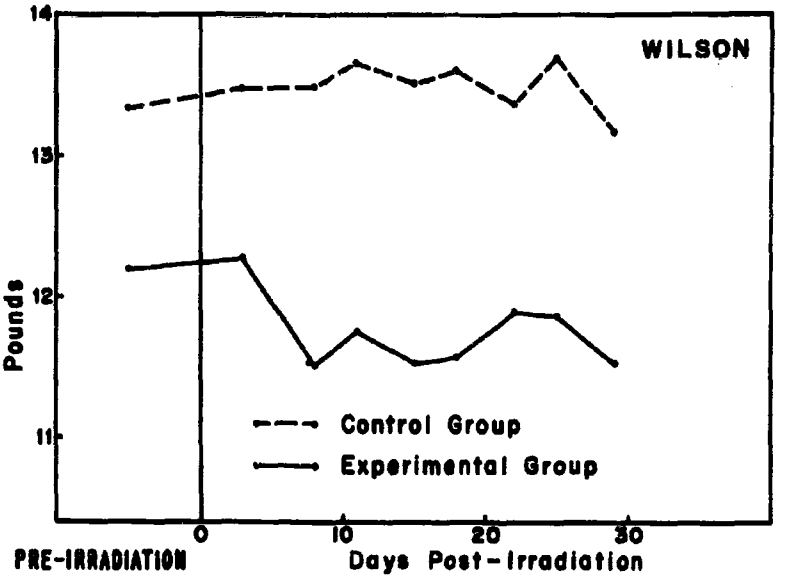


Fig. 3.9—Incidence of diarrhea vs. irradiation dose.



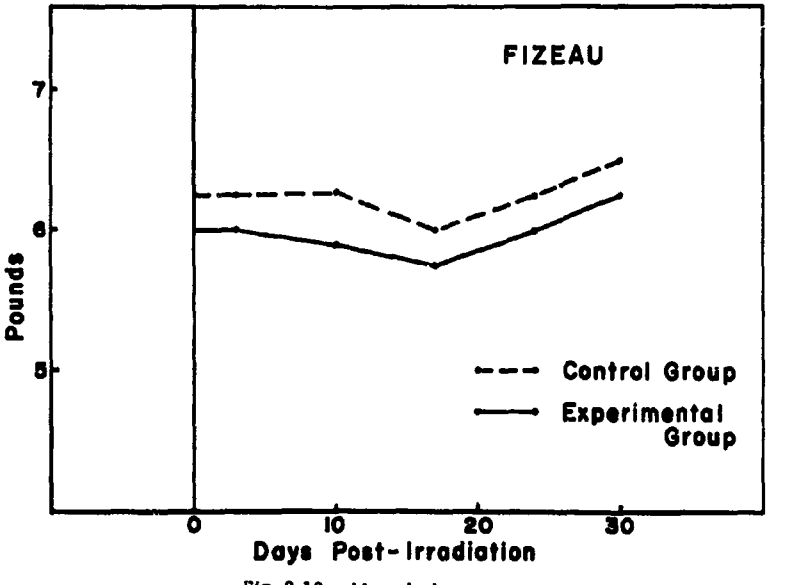


Fig. 3.10—Mean body weight.

TABLE 3.2— Fe^{59} METABOLISM AND HEMATOLOGY, WILSON SHOT*

Day	Fe^{59} uptake, % injected dose in RBC				Plasma Fe, μg %				RBC × 10^6				Hemoglobin, g %				Hematocrit, %			
	C	L	M	H	C	L	M	H	C	L	M	H	C	L	M	H	C	L	M	H
−x					185	216	170	183	5.29	5.33	5.51	6.00	11.0	11.2	11.4	11.9	39.0	39.7	40.6	42.5
1									5.93	5.82	5.86	6.56	12.1	11.7	11.5	12.3	43.9	42.4	41.3	43.9
2	10.7	2.2	2.8	1.4	198	353	288	270	5.69	5.24	5.15	5.56	11.6	10.9	11.0	11.5	40.5	37.8	38.7	39.5
5	83.3	7.7	9.5	6.0	230	440	284	350	5.76	5.51	5.15	6.16	11.8	10.9	10.8	11.3	41.5	39.2	38.2	39.6
8	92.9	9.7	13.2	6.9	194	253	282	283	5.18	5.02	5.04	5.77	10.9	10.7	10.5	10.6	38.9	36.4	36.3	37.5
12	98.7	11.8	13.4	7.2	247	284	258	238	5.45	4.85	5.04	5.25	11.1	9.5	10.3	9.4	40.4	33.5	35.3	34.3
15	96.9	13.1	14.5	4.6	246	328	210	143	5.27	4.30	3.31	2.69	10.8	8.5	6.9	5.2	38.9	30.2	25.8	18.7
19	94.0	11.6	5.9		201	330	170		5.42	3.65	2.41		11.4	7.7	4.5		40.2	27.5	15.0	
22	98.3	12.8	3.8		233	317	210		5.13	3.69	1.71		11.0	7.7	4.3		39.0	27.8	13.5	
24	93.7	14.5	5.8		311	300	215		5.23	4.03	1.84		10.9	9.6	3.6		37.7	25.1	14.0	
26	94.3	14.9	5.7		209	205	160		5.65	3.42	1.59		11.4	6.9	3.6		41.4	26.9	13.5	
29	91.3	17.1	7.3		185	163	85		5.17	3.32	1.71		10.5	7.4	4.1		38.7	26.0	13.5	

Day	WBC				Platelets × 10^4				Polymorphonuclear neutrophils, %				Lymphocytes, %				Reticulocytes, per 100 red cells				Monocytes, %				Eosinophils, %			
	C	L	M	H	C	L	M	H	C	L	M	H	C	L	M	H	C	L	M	H	C	L	M	H	C	L	M	H
−x	8,900	8,540	8,350	9,870					32.6	34	34	27	61	61	61	66												
1	11,883	6,330	6,480	4,870					50	85	86	86	38	14	10	10	2	1	2	1	2	1	1	1	3	0	1	3
2	11,073	2,540	5,330	3,200					50	70	82	77	34	23	15	18	2	1	0	1	4	3	2	3	3	4	1	2
5	9,010	1,450	1,300	1,130	33.8	29.0	37.0	25.7	32	39	55	37	63	58	43	61	2	0	0	0	1	2	1	0	4	1	1	2
8	10,073	1,100	850	850	29.8	14.3	15.3	11.6	42	39	47	34	49	58	51	65	3	0	0	0	4	3	1	0	4	0	1	0
12	8,846	480	450	500	36.4	3.8	4.7	4.7	43	16	21	7	49	83	78	93	3	0	0	0	2	0	0	0	3	0	0	0
15	11,630	410	330	160	40.7	2.3	1.3	3.0	36	25	7	1	48	72	92	99	3	1	0		3	0	0	0	5	0	0	0
19	8,307	380	350		42.5	2.7	5.0		32	10	15		63	89	89		3	1	0		3	1	0		4	1	0	
22	10,653	900	500		33.9	5.5	1.0		30	16	35		63	80	60		3	3	1		2	1	0		3	1	0	
24	11,307	3,750	1,400		35.9	7.5	4.0		34	61	59		60	34	37		2	3	1		2	2	4		3	1	0	
26	10,885	2,820	1,250		34.9	14.5	7.0		30	57	61		64	36	30		4	6	1		2	2	7		2	1	0	
29	9,229	3,625	5,850		49.5	22.0	4.0		34	53	97		58	38	3		6	23	5		7	2	0		4	1	0	

*−x row = grand mean all preirradiation values for the groups.
All values are means for the animals alive in the group at that time.
Day O = day of irradiation = 18 June.
C = concurrent controls.
L = low dose = 410 rads.
M = middle dose = 462 rads.
H = high dose = 520 rads.

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Fig. 3.11—Iron uptake in red blood cells.

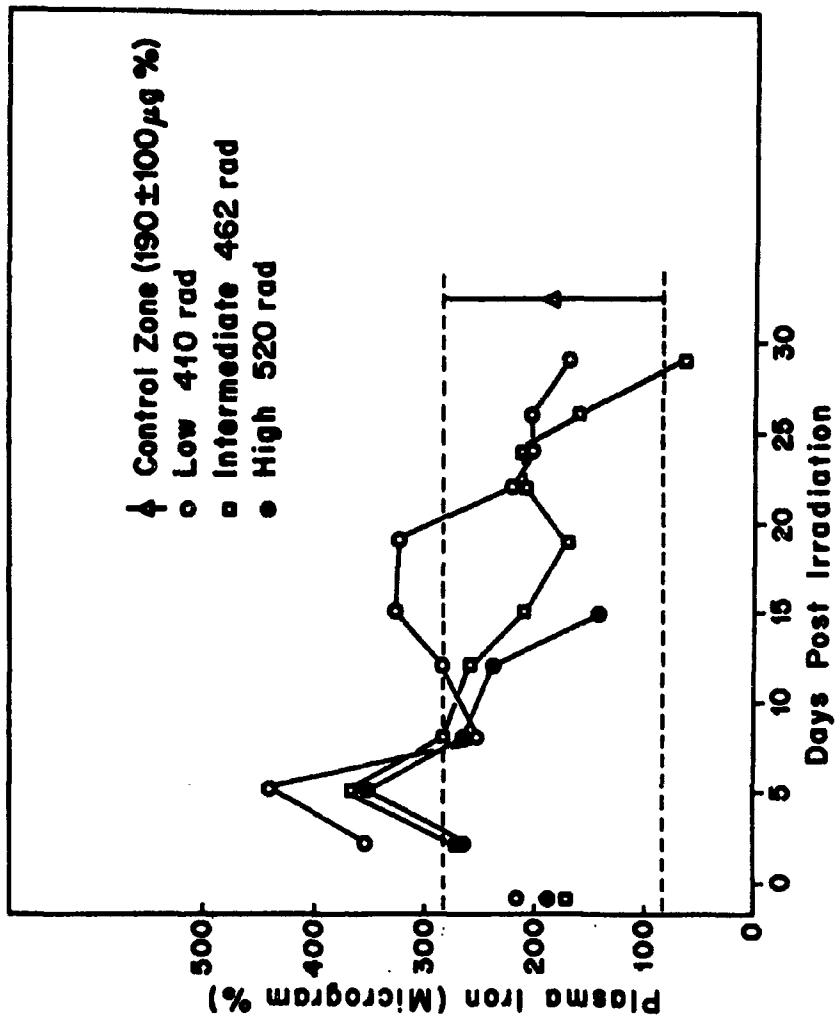

Fig. 3.12—Plasma iron.

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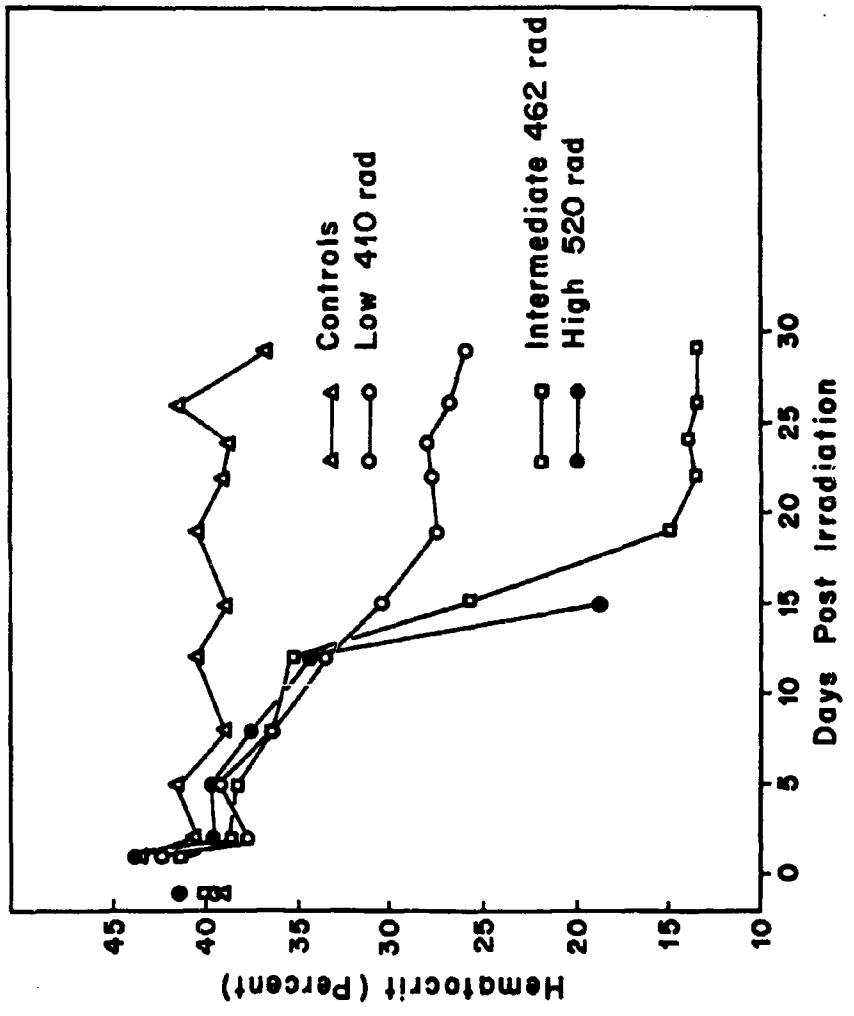

Fig. 3.13—Hematocrit.

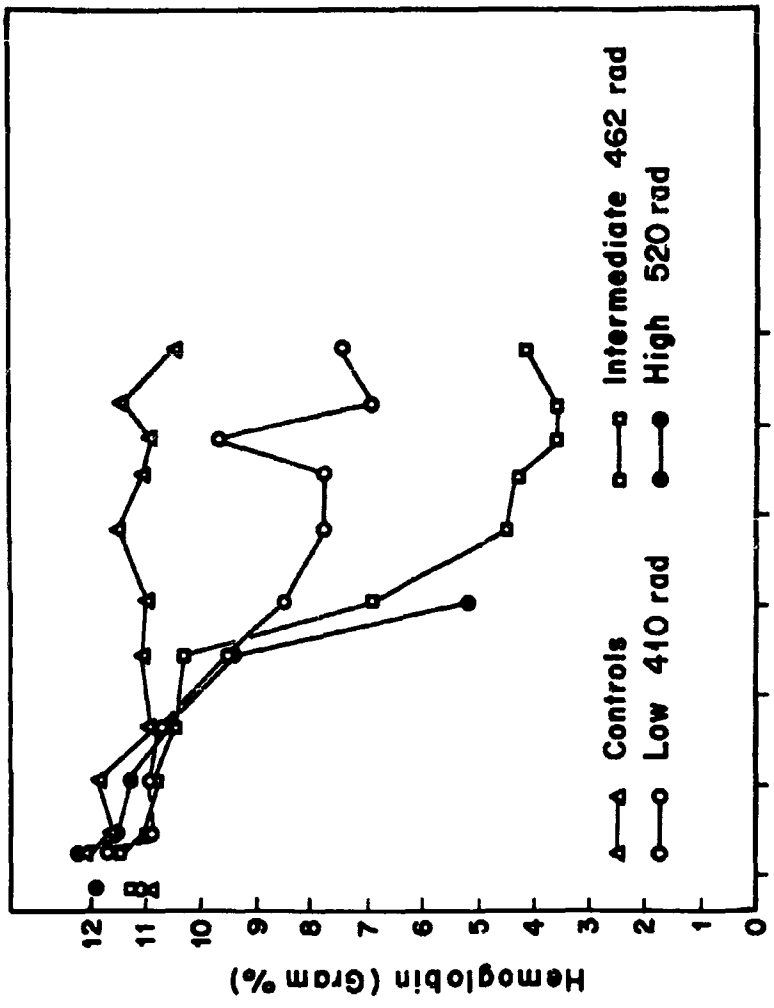

Fig. 3.14—Hemoglobin.

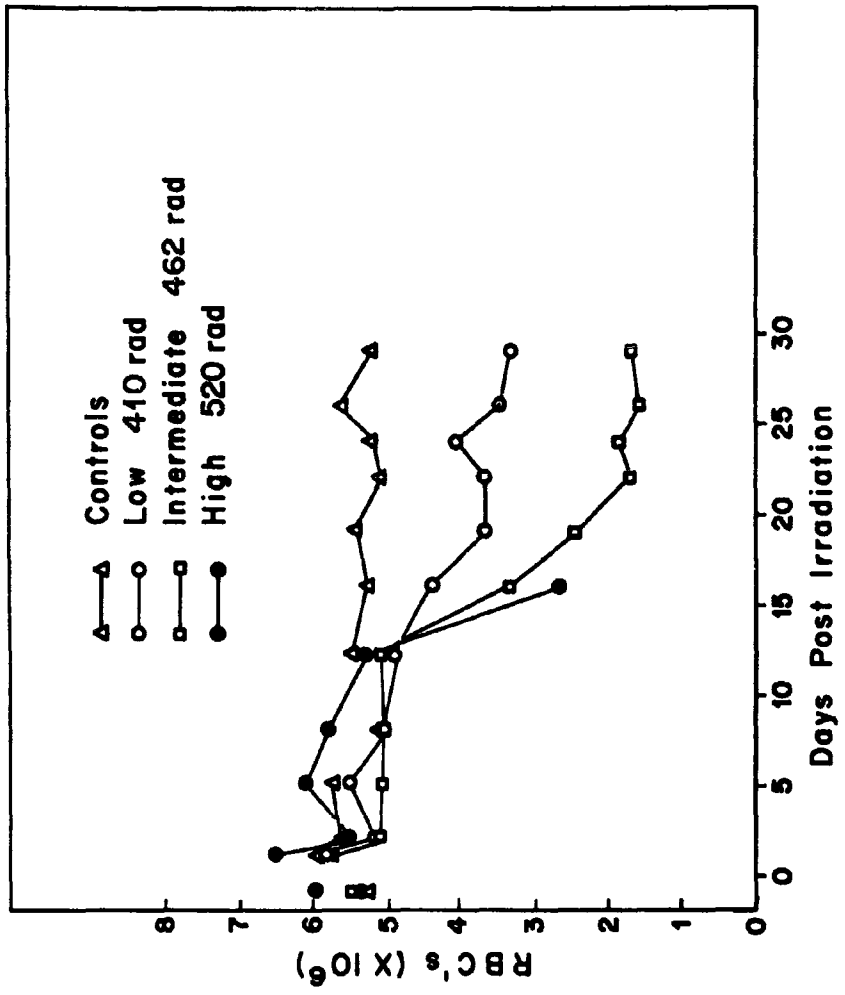

Fig. 3.15—Red blood cells.

the last occurring on the 46th day. The distribution of deaths is shown in Figs. 3.1 to 3.3.

The pathological findings in the animals dying 10 to 17 days postirradiation were fairly uniform, with two exceptions. In the first five animals to die, there was severe hemorrhagic and ulcerative proctitis. This condition was present to a mild degree in one animal dying on the 13th day, but it was not seen thereafter. The other exception was subcutaneous edema and hemorrhage. The majority of the animals dying on the 13th and 14th days had moderate to severe subcutaneous hemorrhage and/or edema. The uniformity of the lesions lends itself to a discussion of the animals as a whole.

After the 17th day there was a marked change in the nature of the lesions found at autopsy. However, with the exception of the last animal to die, they will be discussed with the remainder of the experimental animals since they graphically illustrate the pattern of attempted recovery. The last animal to die (No. 46-22) is discussed in Sec. 3.1.5(j).

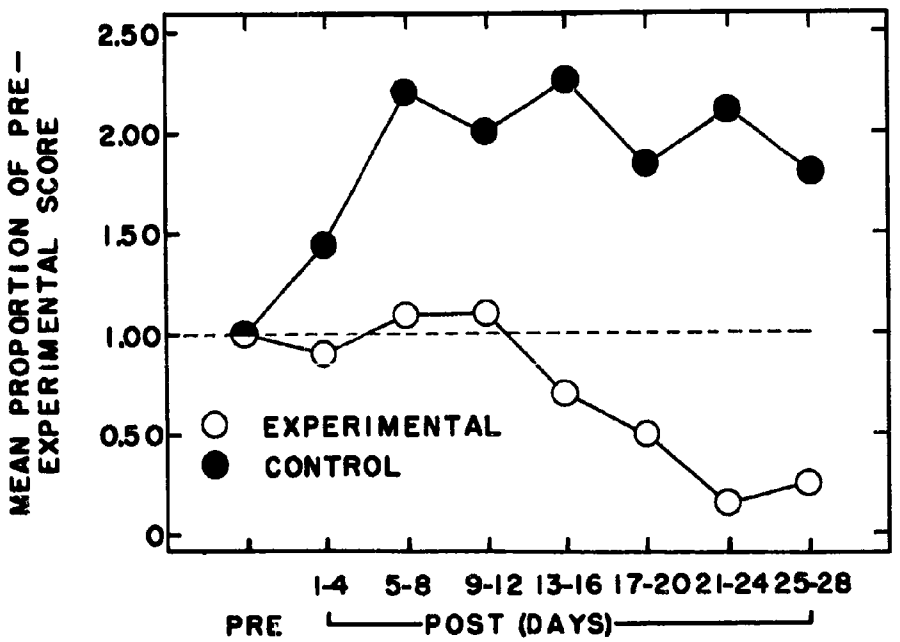

Fig. 3.16—The mean proportional change per observation per four-day period, after the time of nuclear detonation exposure, in nondirected locomotor activity by animals exposed to a nuclear detonation and by control animals.

(a) *Bone Marrow.* The initial response of the bone marrow to this single acute, lethal dose of ionizing radiation was intense vascular congestion and almost complete loss of myeloid and nucleated erythroid cells. The marrow from the femur contained only rare nucleated cells, and that from the sternum and vertebrae contained few more. Even in view of the massive tissue destruction, nuclear debris and macrophage activity were almost completely absent.

Marrow smears stained with Wright's stain were available for morphologic study. The predominant remaining cells were reticulum cells, plasmocytes, and plasmacytoid cells. There were moderate numbers of myeloid and erythroid cells. There were occasional well-preserved megakaryocytes in the bone-marrow sections of the first animal to die, but thereafter their appearance was sporadic.

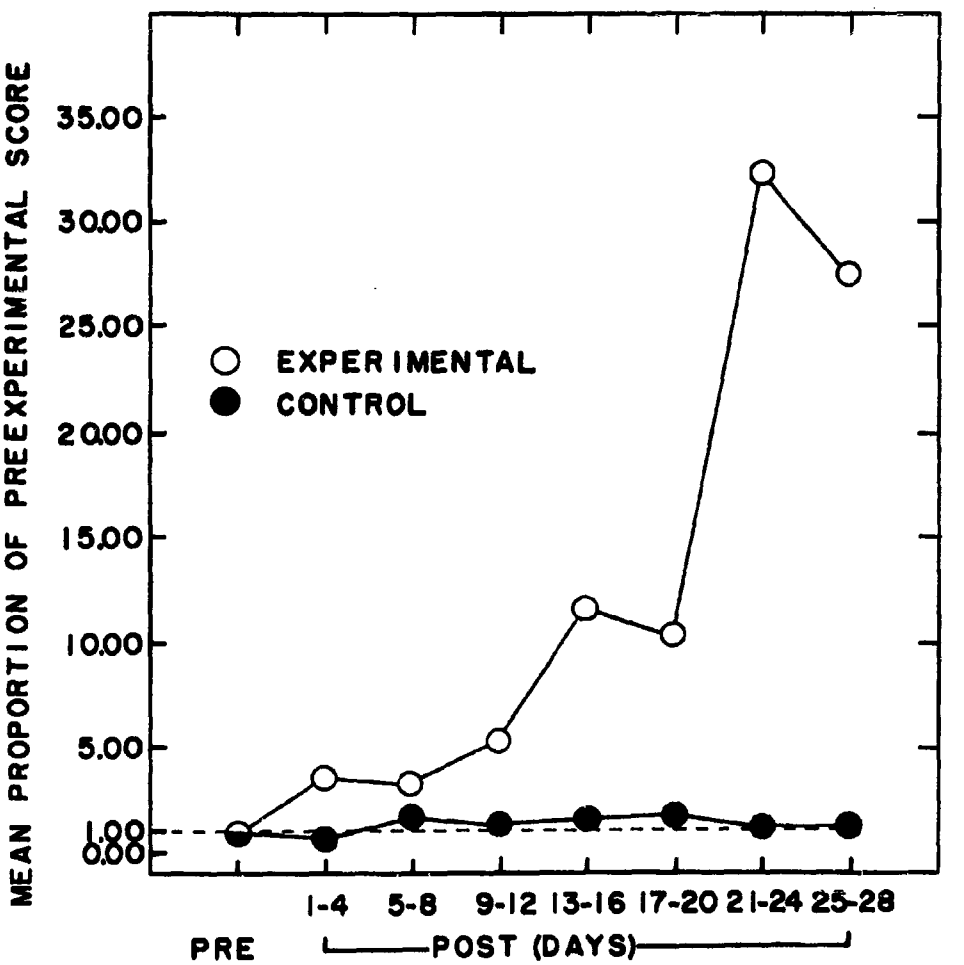

Fig. 3.17—The mean proportional change per observation per four-day period, after the time of nuclear detonation exposure, in object-directed activity by animals exposed to a nuclear detonation and by control animals.

In two animals dying on the 14th day, there was moderate regeneration of myeloid and erythroid elements. However, prominent and consistent regenerative activity did not appear until the 17th day. Although there was definite regenerative activity in the marrow of the animal dying on the 17th day, the marrow was still markedly hypocellular.

One animal each died on the 22d, 26th, and 46th days, and in these instances the marrow was hyperplastic. Erythroid hyperplasia predominated over myeloid hyperplasia. Nuclear and cytoplasmic abnormalities were common in the proliferating cells. Often the chromatin was coarse and irregularly distributed. Cytoplasmic vacuolization was prominent, and there were occasional nuclear vacuoles. There were scattered blasts with multilobed nuclei. Occasional binucleated erythrocytes were encountered. There was stippling of the cytoplasm of the erythrocytes.

Megakaryocytes were unusually prominent. They were often extremely large and contained multiple nuclei.

The bone marrow of four of the animals dying on the 12th, 13th, and 14th days contained scattered colonies of bacteria. These animals also exhibited other evidences of bacteremia.

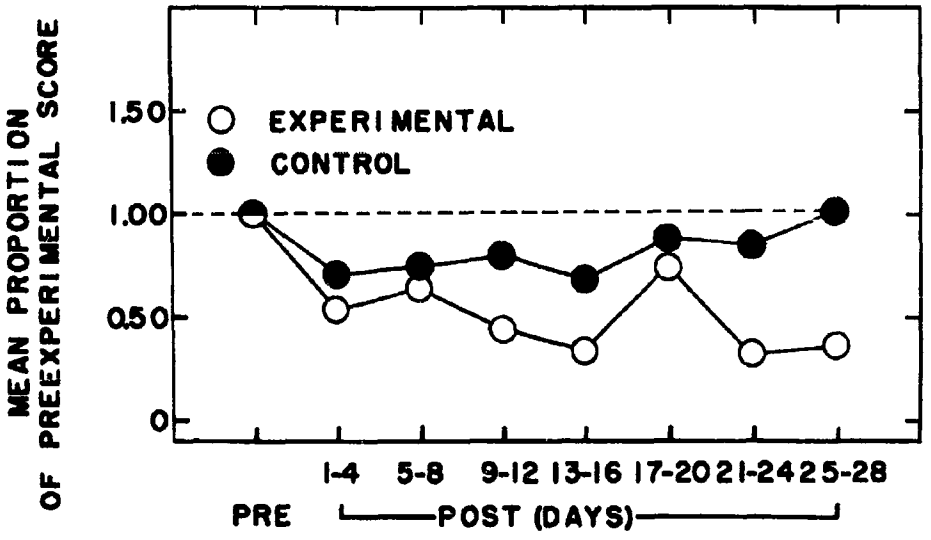

Fig. 3.18 — The mean proportional change per observation per four-day period, after the time of nuclear detonation exposure, in self-directed activity by animals exposed to a nuclear detonation and by control animals.

(b) *Spleen.* The most prominent single change in the spleen was the marked loss of lymphocytes. This involved not only the malpighian bodies but also the red pulp. Even in the last animal to die, the red pulp contained a few normal lymphocytes. For the most part the cells of the red pulp were atypical monocytes with large pleomorphic pale-staining nuclei. Plasma cells were prominent in some cases, but they were not a constant finding. In contrast, the malpighian bodies made a relatively rapid recovery. Although at first the bulk of the cells surrounding the central arterioles were atypical monocytes similar to those scattered through the red pulp, moderate numbers of normal-appearing lymphocytes were making their appearance by the 13th day. Atypical monocytes with giant, bizarre nuclei often persisted. Mitotic figures were scattered throughout the red pulp and the malpighian bodies in every case, and a rare tripolar configuration was seen.

The reticulum framework of the spleen showed little change in character. In the first three cases there was moderate fragmentation and thickening of the reticulum strands of the malpighian bodies; thereafter the reticulum network appeared intact. In addition, as regeneration proceeded, the reticulum fibers became more widely separated so that the spleen appeared as a loose network of fibers, in contrast to the dense collapsed appearance it had on the 10th, 11th, and 12th days.

Although there were occasional small amorphous masses of necrotic material found in several of the spleens, none could be identified as necrotic or thrombosed vessels. Each spleen was examined by means of Masson's and reticulum stains, and in every instance the histologic structure of the arteries and arterioles appeared normal. This included the internal elastic lamella, as well as the media lamella. The necrotic material stained red with periodic acid Schiff stain. There was no thickening of the intima, and no subintimal collections of material were seen.

Hemosiderin deposition was inconstant in severity and occurrence. In several cases there were moderate deposits without regard to group or time of death. On the other hand, spleens without increased hemosiderin were as common as those with abnormal amounts.

In 13 of the 22 animals the spleens contained scattered colonies of bacteria. Both gram-negative and gram-positive bacilli and cocci were present. At times the colonies were inconspicuous, but often they were large and were surrounded by necrotic tissue. In one case there was massive necrosis of the splenic tissue with overwhelming bacterial infiltration.

(c) *Gastrointestinal Tract.* The gut lesions in all the animals were fairly constant in their histologic appearance. Generally the most severe lesions were found in the colon. Except for one animal dying on the 13th day and the last three animals to die, every animal had some degree of acute ulcerative colitis. The severity of the lesions did not parallel groups or day of death.

Generally the initial lesion appeared to be submucosal hemorrhage. Subsequently there was coagulation necrosis of the overlying epithelial cells. Often the lamina propria of the mucosa would remain intact after the epithelium had disappeared. In the early stages the ulcerations were superficial. In one instance there was necrosis of the mucosa, but the muscularis mucosa remained histologically intact. Occasionally tissue necrosis extended through all layers of the bowel wall. Hemorrhage in the damaged areas was often prominent. Bacterial invasion of the ulcerated areas occurred early in the course of the disease. At first bacteria occupied only the ulcerated areas, but subsequently it spread through the adjacent portions of the intestinal wall. The lymphatics became packed with bacteria, and the sinuses of the regional lymph nodes contained large colonies.

The small intestine contained no ulcers. In a rare instance there was an occasional petechium. There was no edema or epithelial change.

Frank gastric ulceration was present in only two instances. However, hemorrhagic gastritis of a moderate degree was found in all but five animals. The usual picture was that of moderate petechiation in the pyloric region. Occasionally petechiae extended into the body and fundus of the stomach. Rarely there were large confluent aggregates of petechiae. In the ulcerated areas bacterial invasion similar to that observed in the colon was often seen.

There was one duodenal ulcer similar to those seen in the colon. Tissue necrosis had involved all portions of the duodenal wall, with subsequent perforation of the gut wall. The inflamed periduodenal tissue was adherent to the liver.

In five of the six animals dying on the 11th, 12th, and 13th days, there was severe hemorrhagic and ulcerative proctitis. However, this condition was seen in only one other animal; in that instance it was mild and occurred on the 13th day.

(d) *Lymph Nodes.* In none of the animals were the lymph nodes spared from the sweeping pathological changes produced by irradiation. There was some variation in the severity of the lesions observed from case to case, but this did not appear to correlate with dosage or day of death. It was generally true that the lymph nodes from the body cavities were more severely affected than the axillary or inguinal lymph nodes. The submandibular nodes were often severely affected.

In the acute stages the capillaries of the lymphoid tissue were greatly dilated and were filled with protein-rich fluid. Lymphocyte-like cells with small dark-staining nuclei were scattered throughout the nodes. In many areas there was dense chromatin dust scattered loosely in the reticulum. In many lymph nodes no germinal centers remained.

A circumstance peculiar to those nodes containing large numbers of bacteria was an infarcted appearance. In many instances the peripheral sinuses were filled with bacteria. There was extensive hyaline necrosis of the stroma, and remaining nuclei were in various stages of degeneration. Bacteria were numerous in all lymph nodes draining ulcerated epithelial surfaces.

(e) *Lungs.* Typically the lungs were pink and crepitant. Small fresh hemorrhages from 2 to 6 mm in diameter were scattered throughout all portions of the parenchyma, but there was a striking tendency for them to occur around lung mites. The hemorrhagic areas were free of leukocytes, except when they were associated with lung mite cysts. In these instances the degenerating leukocytes were presumed to have been present prior to irradiation and were in various stages of degeneration. In only one instance was the hemorrhage regarded as being extensive enough to interfere with respiration.

Bacterial infiltration of the lungs was often severe and was found in as many cases as pulmonary hemorrhages. However, the bacterial colonies were not so numerous as the hemorrhages. In several instances bacteria were present only in the pulmonary capillaries and venules; typically, however, they were scattered throughout the parenchyma. Many of the colonies were surrounded by bands of tissue necrosis. In addition, it was unusual to find an area of tissue necrosis devoid of bacteria.

In one animal there was moderate neutropenic pneumonia. In several others there were small localized areas of interstitial and intra-alveolar edema. The animals dying on the 22d and 26th days had extensive necrotizing pneumonia, with heavy infiltration by large mononuclear cells. There were small numbers of mature neutrophils. Two of the animals had areas of pulmonary infarction.

(f) *Liver.* In 8 of the 22 animals the liver contained scattered colonies of bacteria. Often the colonies were limited to the sinusoids and portal veins. Occasionally, however, they were scattered throughout the parenchyma. Central necrosis was observed in five of the animals; in three of the animals it was minimal, but in two of the animals it was massive. The areas of necrosis were confluent, and the only intact cells that remained were in the area immediately adjacent to the portal canals. In four instances the areas of necrosis were infiltrated by bacteria.

(g) *Genitalia.* Both female and male monkeys were used in the experiment. Unfortunately none of the monkeys were sexually mature. In no case could changes in the testicle be found which could be associated with irradiation. In the ovary a rare degeneration ovum could be found, but the majority were intact.

(h) *Skin.* The most typical finding was mild petechial hemorrhage. In 8 of the 13 animals dying on the 13th to the 17th day, there was severe localized subcutaneous edema. In five instances the edema was accompanied by subcutaneous hemorrhage. Both the upper and lower extremities were frequently involved. Frequently there were small excoriations of the epidermis over the edematous and hemorrhagic areas. The soft tissues of the neck and face were often involved by edema, and in one instance there was massive subcutaneous hemorrhage over the left side of the face. This lesion was observed from its beginning as a small pea-sized ecchymosis which, over a period of two days, spread to involve the entire side of the face.

Focal hyaline necrosis of the epidermis and dermis was common in the edematous and hemorrhagic areas. The damaged tissue was devoid of inflammatory cells but was frequently infiltrated by bacteria.

(i) *Mouth.* The mouth was frequently the site of small superficial ulcerations. These were associated with gingival ecchymoses and perioral edema and ulceration. Six of the animals had moderate to severe hemorrhage in the mucosa of the tongue.

(j) *Others*. A constant finding was mild petechial hemorrhage over the epicardium. In several animals there was moderately severe hemorrhage in the epicardium of the right atrium. There was no myocardial or endocardial hemorrhage.

Mild cloudy swelling of the tubules was occasionally seen in the kidneys. When there was generalized bacteremia, the kidneys would often contain scattered colonies of bacteria in the capillaries and venules. In these cases the adrenals also on occasion contained small petechiae and minute colonies of bacteria.

In one animal there was necrosis of the pancreas, and one animal had moderately severe hemorrhagic cystitis.

The brain, thyroid gland, and parathyroid glands were devoid of lesions attributable to irradiation.

Animal 46-22 was interesting in several respects. First, the long time lapse between irradiation and death was unusual in view of the massiveness of the dose. Second, the anatomical lesions offered a challenge in interpretation.

From a hematological point of view, there had been almost complete recovery from the effects of irradiation. The white counts and erythrocyte counts of the peripheral blood were within the range of normal; however, there were occasional nucleated red cells present. Similarly, the platelet count was adequate. Morphologically the platelets appeared larger than normal.

The bone marrow was hyperplastic, with the erythroid series predominating. There was active regeneration of the lymphoid tissue, but this did not appear to be proceeding at so rapid a rate as the regeneration of the bone marrow.

There were no intestinal lesions. There was no subcutaneous hemorrhage, but there were chronic cutaneous ulcers of the extremities. There was a rare focus of recent hemorrhage in the lungs.

The most prominent finding was the marked distention of the urinary bladder. This appeared to be due to the marked localized edema of the prepuce and skin of the genital region. Although there was no hydro-ureter, there was mild dilatation of the collecting tubules of the kidneys. It seems probable that urinary retention contributed greatly to the animal's death. Additional findings were moderate emaciation and advanced epilation.

The experimental design for shot Wilson was identical to the Fizeau procedure. As a result the anatomical lesions were much the same. However, there was one important difference. Owing to physical factors involved in the experiment, the animals in groups A, B, C, and D of Wilson received far more radiation than any of the Fizeau animals. Consequently, a slightly different mode of death was observed.

Wilson groups A and B received sufficient radiation to produce "gastrointestinal death." This was manifest by (1) relatively rapid death (5 to 10 days postirradiation), (2) a paucity of hemorrhagic phenomena, and (3) primary radiation damage to the epithelial cells lining the small intestine and colon.

Only one animal each from groups A and B exhibited skin petechiation. In addition, there were no oral lesions nor was there evidence of bacteremia. All the animals exhibited colonic ulceration and epithelial atypism similar to that observed in the 1500-r animals exposed at the Southwest Research Institute. None of these animals survived past the 11th day. Figure 3.3 shows the temporal death pattern of total number of animals.

Group C was borderline between "gut death" and "bone-marrow death." The anatomical material was not adequate to indicate, with any degree of surety, the exact mode of death. However, from the temporal pattern of death, it appears probable that both modes of death were present.

All animals dying in groups D through I expired as a result of bone-marrow failure. Secondary colonic ulceration was present in every animal as was gastric ulceration. Oral ulcerations with facial edema, skin hemorrhages, and widespread bacterial infiltration were present in all but 5 of the 53 animals dying in these groups.

From these data it can be concluded that 1000 rem of mixed ionizing radiation, administered under the conditions of this experiment, is sufficient to induce gut death in the Macaca

mulatta monkey. This conclusion is certainly supported by the mode of death exhibited by the animals in groups A and B of Wilson shot.

3.2 PHYSICAL MEASUREMENTS

3.2.1 Neutron Dose

The neutron-flux measurements are summarized in Table 3.3. These data give fluxes in the intervals 0.3 ev (thermal), greater than 4 kev, greater than 750 kev, greater than 1.5 Mev,

TABLE 3.3—NEUTRON THRESHOLD-DETECTOR MEASUREMENTS*

Station	Slant range, yd	Measured flux, neutrons/cm²				
		Thermal F_{Au}	F_{Pu}	F_{Np}	F_U	F_S
			Wilson			
A	1335	9.84×10^{10}	2.73×10^{11}	1.11×10^{11}	5.2×10^{10}	2.37×10^{10}
B	1360	8.02×10^{10}	2.28×10^{11}	1.05×10^{11}	5.0×10^{10}	1.94×10^{10}
C	1385	1.04×10^{11}	2.06×10^{11}	9.2×10^{10}	4.28×10^{10}	1.95×10^{10}
D	1410	6.41×10^{10}	1.86×10^{11}	8.0×10^{10}	3.95×10^{10}	2.17×10^{10}
E	1435	6.39×10^{10}	1.62×10^{11}	7.7×10^{10}	3.52×10^{10}	1.56×10^{10}
F	1460	5.39×10^{10}	1.32×10^{11}	5.62×10^{10}	3.1×10^{10}	1.71×10^{10}
G	1484	4.88×10^{10}	1.05×10^{11}	4.46×10^{10}	2.6×10^{10}	1.52×10^{10}
H	1509	2.03×10^{10}	1.17×10^{11}	4.5×10^{10}	2.55×10^{10}	1.31×10^{10}
I	1534	3.44×10^{10}	8.8×10^{10}	2.73×10^{10}	2.0×10^{10}	1.15×10^{10}
			Fizeau			
A	1435	6.06×10^{10}	1.29×10^{11}	5.72×10^{10}	2.63×10^{10}	1.45×10^{10}
B	1460	5.70×10^{10}	1.24×10^{11}	6.20×10^{10}†	3.90×10^{10}	1.01×10^{10}
C	1484	4.83×10^{10}	1.08×10^{11}	5.20×10^{10}	2.16×10^{10}	1.14×10^{10}
D	1509	4.85×10^{10}	9.38×10^{10}	4.69×10^{10}†	2.01×10^{10}	7.30×10^{9}
E	1534	3.73×10^{10}	7.48×10^{10}	4.15×10^{10}	1.57×10^{10}	8.23×10^{9}
F	1559	3.21×10^{10}	6.30×10^{10}	3.15×10^{10}†	1.46×10^{10}	7.58×10^{9}
G	1584	2.59×10^{10}	5.47×10^{10}	3.03×10^{10}	1.28×10^{10}	6.84×10^{9}
H	1609	2.42×10^{10}	5.60×10^{10}	2.30×10^{10}	1.27×10^{10}	4.23×10^{9}
I	1634	2.07×10^{10}	4.00×10^{10}	2.30×10^{10}	1.04×10^{10}	5.08×10^{9}
J	1659	1.69×10^{10}	3.88×10^{10}	1.94×10^{10}	9.23×10^{9}	3.80×10^{9}

*F_{Au}, flux as measured with gold foils; F_{Pu}, plutonium foils; F_{Np}, neptunium foils; F_U, uranium foils; and F_S, sulfur foils.

† Calculated flux (no foils available.)

and greater than 2.5 Mev. The neutron doses calculated from a least-squares fit of these data are listed in Table 3.1. The values were calculated using

$$\text{Dose} = 10^{-9} (0.7F_S + 0.7F_U + 1.5F_{Np} + F_{Pu} + 0.029F_{Au})$$

3.2.2 Gamma Dose

The gamma dose measurements, determined by the USAF chemical dosimeter, are listed in Table 3.1 for both Wilson and Fizeau shots. The details of exposure, as well as dose response vs. distance curves, are reported[1] by Project 39.1.

3.2.3 Gold Activations

The results of the activations of the various types of gold inlays are shown in Table 3.4. The thermal neutrons are not only those initiating from the weapon but also those produced

by the fast neutrons being degraded in tissue; therefore the values given represent the total thermal-neutron contribution.

TABLE 3.4—GOLD ACTIVATION

Group	Slant range, yd	Measured flux	Dose, rep
A	1335	7.28×10^{11}	364
B	1360	6.03×10^{11}	301
C	1385	5.50×10^{11}	279
D	1410	4.31×10^{11}	216

REFERENCE

1. S. C. Sigoloff et al., Operation Plumbbob Report, ITR-1500, May 1958.

Chapter 4

DISCUSSION*

4.1 GENERAL

With the weapons and weapons systems of the future extending biologically permissible levels of exposure to the limit of present-day knowledge, every effort must be made to take advantage of all available data of importance in understanding the radiation syndrome, as well as defining certain threshold doses of radiation vs. undesirable biological responses. Although for many years animal experiments have furnished general conclusions, specific responses as they compare to man have been lacking. Over the past 10 years considerable human data have been accumulated from among the Japanese survivors, accidentally exposed individuals, and certain selected cancer patients receiving therapeutic radiation. In addition, a vast store of laboratory data has been accumulated on the monkey in both acute and chronic radiation exposure situations. Since the monkey in so many instances evidences the same biologic response to ionizing radiation as the human, it is indeed the animal of choice in attempting extrapolation of dose vs. effect on man. Exposures on Wilson and Fizeau shots clearly demonstrate a situation not too different from that of the Japanese detonations, and the radiation follow-up defines a remarkable similarity between the "typical" acute radiation syndromes.

In man, exposure to a sufficient amount of penetrating X ray, gamma, and/or neutron irradiation causes characteristic clinical sequelae, the acute radiation syndrome. This complexity of signs and symptoms, unfolding along a rather fixed time schedule, forms a peculiar picture that is as well defined as other clinical entities. The most conspicuous features of the typical radiation-induced disease are as follows:

Within 2 hr following exposure gastrointestinal complaints develop rather abruptly; anorexia, nausea, and malaise are predominant and are accompanied by listlessness, drowsiness, and fatigue. The deterioration of general condition progresses rapidly and leads to profuse vomiting, extreme weakness, or even prostration. This early reaction culminates about 8 hr after exposure and then subsides rather quickly. On the second postirradiation day nausea and occasional vomiting still persist, but the general condition is markedly improved; and on the third postirradiation day all complaints have disappeared. This burst of early signs

* From the inception of this program a corollary study to summarize all human data of interest was undertaken. Originally this clinical comparison was intended as an appendix to this report; however, enthusiastic interest evidenced by the American Medical Association and the Office of the Surgeon General, USAF, dictated an early and separate unclassified publication. A majority of the effort and credit goes to Dr. H. B. Gerstner of the Department of Radiobiology for his contributions. Much of the material in this discussion has been taken directly from that report.[1]

and symptoms might be conveniently designated as the "initial reaction" or as the "prodromal phase" of the acute radiation syndrome in order to avoid confusion. After dissipation of the prodromal effects the patient is relatively asymptomatic and capable of performing normal work or even of enduring strenuous physical exertion. This favorable state, the "latent period," may extend to the 19th and 20th postirradiation days, when a new phase is entered rather abruptly. The patient experiences chills, malaise, fatigue, and shortness of breath upon exertion, similar to the acute onset of an infectious disease. Again the general condition deteriorates rapidly, and within 2 or 3 days hospitalization becomes necessary. Manifestations of severe bone-marrow depression, characterized hematologically by leukopenia, thrombocytopenia, and anemia, appear in the form of frank hemorrhages, purpura, susceptibility to infection (especially in the oral cavity), fever, and other signs and symptoms associated with such disorders of the blood picture. This phase of aplastic anemia culminates on about the 30th day, when the patient passes through a critical state. Thereafter recovery slowly develops; it becomes obvious between the 40th and 50th days; fever disappears, infectious lesions in the oral cavity heal, and the blood picture approaches normal values. Convalescence begins after the 60th day and is followed by resumption of work and normal life approximately three months postexposure.

According to this chronologic sequence four distinct states of the acute radiation syndrome can thus be established, namely, prodromal, latent, bone-marrow depression (or aplastic anemia), and recovery phases[1] (Fig. 4.1). Of course, the typical disease as outlined above will be subject to variation and modification attributable in man to two factors: dose and individual susceptibility. The following comments will perhaps emphasize the limited, yet meaningful, interpretations that may be made today in comparing field results with certain human data.

4.2 LETHALITY

Among the Japanese studies no accurate data are available on mortality rates; therefore the present experiment perhaps can contribute toward a better LD_{50}^{30} for man. From shot Wilson, analysis of the limited data did permit an excellent pilot study, and the results enabled a more accurate placement of animals on shot Fizeau. From an analysis of only groups G, H, and I on Wilson, an LD_{50}^{30} of 473 rem was computed by means of probit analysis. Of further interest is the incidence of mortality. The Japanese data show two early peaks, disregarding the first day, a peak during the first 10 days and a peak during the third 10-day period; whereas the monkeys demonstrated peaks on the 7th and 14th days postirradiation, with 14 per cent of the deaths occurring on the 7th day and 13 per cent on the 14th day. Analysis of the Fizeau experiment (27 per cent mortality) yields an LD_{50}^{30} of 522 rem. When the mean log survival time for large groups of animals is plotted as a function of dose, three distinct breaks in the curve are apparent, suggesting three distinct pathogenic mechanisms (Fig. 4.2). Death is probably caused in the low-dose range by hematopoietic depression, in the middle-dose range by gastrointestinal denudation and inflammation, and in the high-dose range by failure of the central nervous system.[2] In man the hematopoietic form of the disease is rather well established, based on a reasonable number of observations; the gastrointestinal form is but slightly documented since only two recorded nuclear accidents fall into this dose range and since the Atomic Bomb Casualty Commission data on early cases are not complete; and the cerebral form is completely unrecorded since persons who were close enough to the hypocenter to experience such doses were also subject to overwhelming thermal and blast injuries. In the chaos of Japan, even though there were no reliable clinical observations in such early deaths, clinical patterns were determined on patients who survived for a few days and in whom other injuries were of secondary importance; therefore there is a potential reservoir of much needed human data.

4.3 VOMITING

The earliest symptoms in the monkeys and the many exposed humans were nausea and vomiting. In the 30-day survivors the incidence of vomiting was 39 per cent for both the Wilson

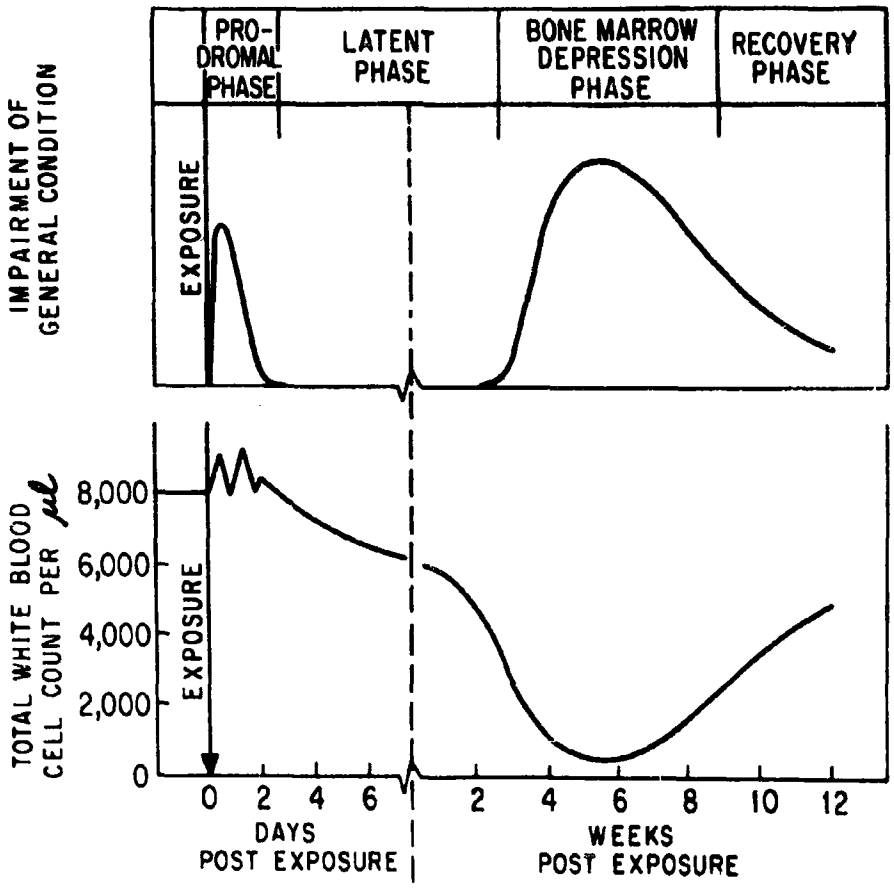

Fig. 4.1—Acute radiation syndromes.

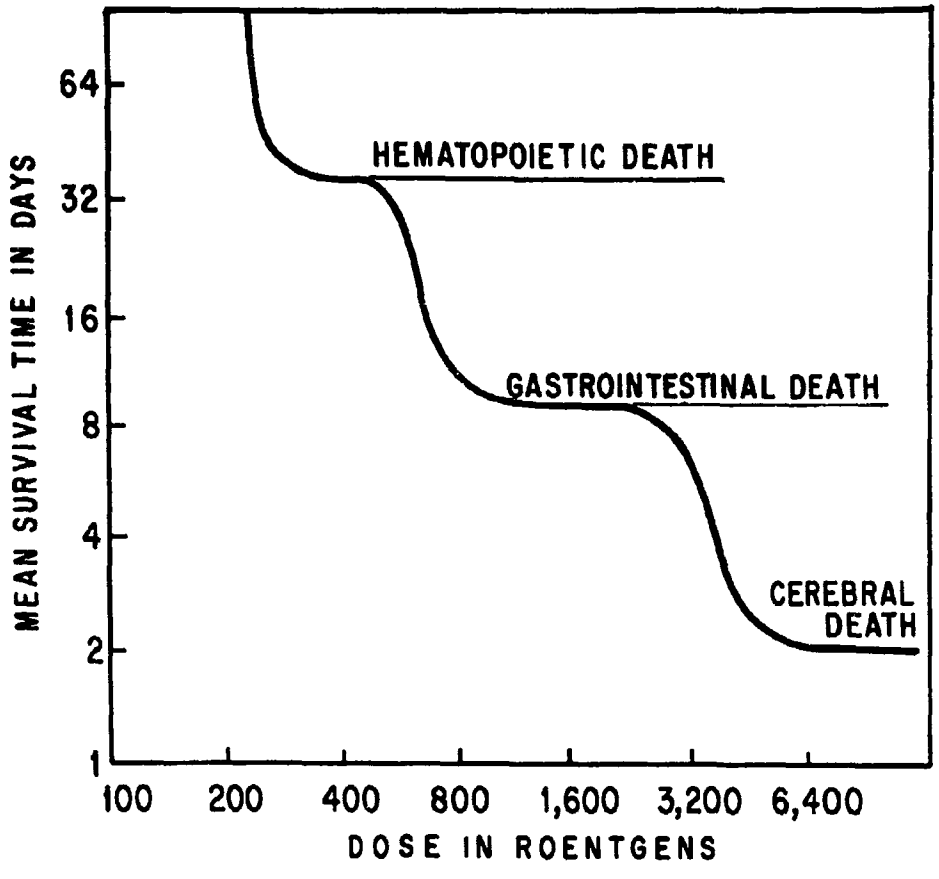

Fig. 4.2—Mean survival time vs. dose.

and Fizeau animals (Fig. 3.5). In 30 cases of therapeutic radiation, 200 r of whole-body X radiation produced nausea and vomiting in 35 per cent of all individuals treated.

4.4 IRON METABOLISM AND HEMATOLOGY

One of the most reliable biologic measures of radiation damage is the drop in leukocyte count. The time course demonstrates a strikingly similar pattern for different exposure situations, as evidenced by Fig. 4.3. Whole-body X ray in therapeutic doses produced a statistically significant drop in the WBC at D+7 day and significance in the lymphocytes on D+2 day with a 0.01 level of confidence.[3] Table 3.2 reveals a similar pattern of response when the lymphocyte is compared with the WBC in that there is an earlier and a more abrupt decline in the lymphocyte. Apparently, ionizing radiation induces in the hematopoietic tissues a given response that then proceeds according to inherent properties of that biological system. This uniformity of response may well be a common denominator for comparing the clinical case histories from monkey experiments and the raw reservoir of data in radiation therapy, as well as the histories from the Japanese. Certainly the Wilson data demonstrate the bone-marrow depression phase of the acute radiation syndrome. In every instance the precipitous drop in hemoglobin, hematocrit, RBC, and plasma iron occurs between 15 and 21 days.

4.5 DIARRHEA

Although diarrhea was frequently observed among Hiroshima and Nagasaki casualties, it is not necessarily a characteristic of the uncomplicated acute radiation syndrome. By the same token, early and persistent diarrhea, when definitely not caused by malnutrition or infection, does suggest radiation injury. Even though certain therapeutic doses to humans clearly show that the symptomatology of diarrhea does not belong to the hematopoietic form of the acute radiation syndrome, the few high-dose accidental exposures, as well as innumerable animal experiments including Wilson and Fizeau data (Fig. 3.9), indicate the presence of severe gastrointestinal damage following exposure to doses of 400 r or more.

4.6 EPILATION

A careful survey of all the human data, excluding the fall-out victims, indicates that epilation occurs when the air dose is in excess of 300 r. It is common radiotherapeutic experience that 300 r is essentially the threshold dose for epilation. This same dose effect is well documented on the monkey using Co^{60}, fast neutrons, thermal neutrons, reactor mixtures of neutron and gamma, and bomb mixtures of neutron and gamma radiation.[2,4,5] This symptomatology is of prognostic value since it is consistently noticeable around 13 to 15 days postirradiation, thus it is a forerunner to the bone-marrow depression phase of the acute radiation syndrome and can serve as a reasonable dosimeter for the future course of the disease—certainly it indicates the need for medical surveillance and, probably, hospitalization. In Wilson shot all the animals were exposed to doses higher than 300 rem, and 100 per cent of the animals experienced epilation; whereas in Fizeau shot 65 per cent of all the animals epilated. (In this particular instance 68 per cent of the animals received 320 rem or more.) Inasmuch as Oughterson and Warren[6] estimated the threshold epilating dose to be 300 rem, this study permits a direct comparison of the parameter of epilation in monkey and man.

4.7 PURPURA

One phase of the radiation response compares with the onset of an infectious disease—the manifestation of malaise, fever, fatigue, and, finally, frank hemorrhage, purpura, and susceptibility to infection. This phase, the bone-marrow depression or aplastic anemia phase,

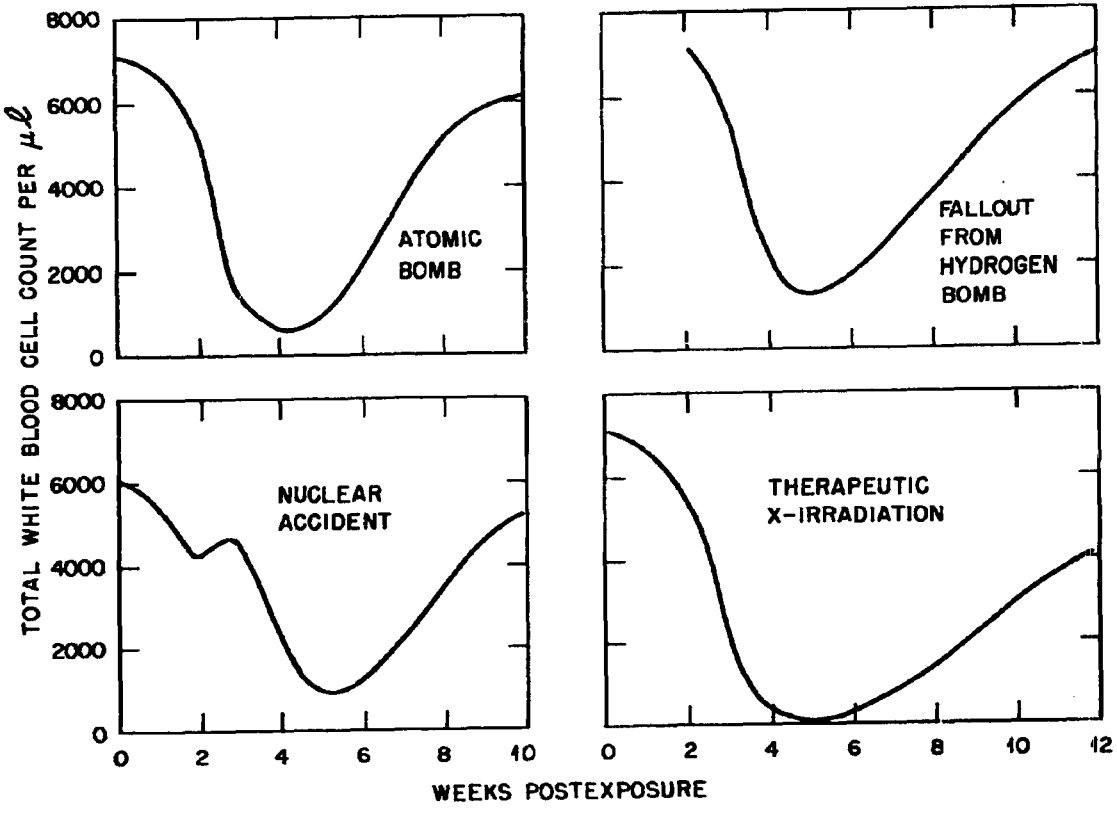

Fig. 4.3—Hematology time-course comparison for different irradiations.

usually requires careful medical surveillance if a favorable prognosis is to be obtained. Purpura developed rather rapidly in these exposed animals, and the clinical course ran for 30 days among the survivors; thereafter, recovery began, and no further deaths were noted.

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Chapter 5

CONCLUSIONS AND RECOMMENDATIONS

Recent world events clearly demonstrate the real potential of nuclear warfare and the inevitable exposure of large masses of people to relatively unknown doses of ionizing radiation. If any order is to come of such chaos, a reasonable understanding of the radiation syndrome as it unfolds must be clearly recognized, and diagnosis and prognosis must be formed by certain guidelines established by laboratory and field research. Present knowledge can contribute to such an understanding and to the delineation of reasonable "best guesses." For example, absence of nausea and vomiting suggests an air dose of 100 r or less; furthermore, it indicates that the clinical course of the disease will be quite mild. Epilation on or about the 13th to 15th day, with signs of purpura and fever, clearly suggests the typical hematopoietic form of the acute radiation syndrome with air doses from 100 to 300 r. Early and persistent diarrhea, when not caused by malnutrition and/or infection, suggests the gastrointestinal disorder and doses more nearly 400 to 500 r. Finally, the early appearance of ataxia, lethargy, convulsions, violent vomiting, nystagmus, etc., evidences the central nervous system involvement with early deaths and a dose range of 2000 r and greater.

Experiments such as those of Program 39 must continue (1) to better delineate the early effects of acute radiation in terms of the biological dose response; (2) to compliment certain human therapeutic data as it unfolds; (3) to further enhance the interpretation given to the records of the Japanese casualties; (4) to study the long-term or latent effects of acute radiation exposure; (5) to determine the difference, if any, between acute exposure vs. the fallout exposure pattern; and (6) to aid in establishing a radiation dose vs. individual susceptibility factor.

Finally, provisions must be made through some national scientific agency to provide for long-term follow-up on all such experiments in order that the potential effects on future generations can be more accurately assessed.

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